

FOR OFFICIAL USE ONLY

ACCESS DB # 181121
PLEASE PRINT CLEARLY

RECEIVED

Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: SABITHA GAZI (STIC) Examiner #: 74141 Date: 3/2/06
 Art Unit: 1616 Phone Number: 2-0622 Serial Number: 10/521,927
 Location (Bldg/Room#): 4A45 (Mailbox #): 4C70 Results Format Preferred (circle): PAPER DISK

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

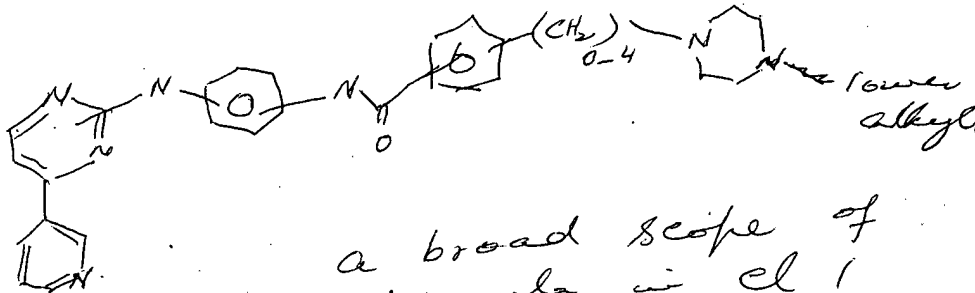
Title of Invention: 4-4(methyl piperazine - - -)Inventors (please provide full names):
James Alexander FaginEarliest Priority Date: 371 of PCT/IB03/01984 5/23/03Search Topic: 5724/02

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the electro species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Ch 1-10

Please search for the compound of
 cl 1 and its method of use



Copy of Chs enclosed

Thank you

STAFF USE ONLY

Searcher: <u>Noble</u>	Type of Search	Vendors and cost where applicable
Searcher Phone #: _____	____ NA Sequence (#)	<input checked="" type="checkbox"/> STN _____ Dialog
Searcher Location: _____	____ AA Sequence (#)	____ Questel/Orbit _____ Lexis/Nexis
Date Searcher picked Up: <u>3/14/06</u>	<input checked="" type="checkbox"/> Structure (#)	____ Westlaw _____ WWW/Internet
Date Completed: <u>3/14/06</u>	<input checked="" type="checkbox"/> Bibliographic	____ In-house sequence systems
Searcher Prep & Review Time: <u>10</u>	____ Litigation	____ Commercial _____ Oligomer _____ Score/Length
Online Time: <u>34</u>	____ Fulltext	____ Interference _____ SPDI _____ Encode/Transl
	____ Other	____ Other (specify)

=> b hcap

FILE 'HCAPLUS' ENTERED AT 14:51:19 ON 14 MAR 2006

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 14 Mar 2006 VOL 144 ISS 12

FILE LAST UPDATED: 13 Mar 2006 (20060313/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all hitstr 144 tot

L44 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2006:15086 HCAPLUS

DN 144:108347

ED Entered STN: 06 Jan 2006

TI Preparation of pyrimidine urea derivatives as kinase inhibitors for use against proliferative diseases

IN Ding, Qiang; Gray, Nathanael Schiander; Li, Bing; Liu, Yi; Sim, Taebo; Uno, Tetsuo; Zhang, Guobao; Pissot Soldermann, Carole; Breitenstein, Werner; Bold, Guido; Caravatti, Giorgio; Furet, Pascal; Guagnano, Vito; Lang, Marc; Manley, Paul W.; Schoepfer, Joseph; Spanka, Carsten

PA Novartis AG, Switz.

SO PCT Int. Appl., 327 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07D-0239/48

ICS C07D-0409/12; C07D-0401/12; C07D-0405/12; C07D-0403/12;
A61K-0031/505; A61K-0031/506; C07D-0251/48; A61P-0035/00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO2006000420	A1	20060105	2005WO-EP06815	20050623
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
	RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			

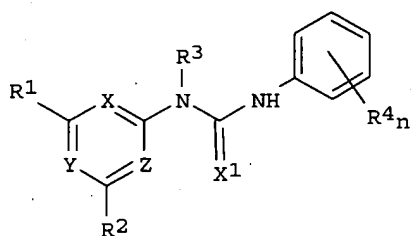
PRAI 2004US-582425P P 20040624

2005GB-0012324 A 20050616

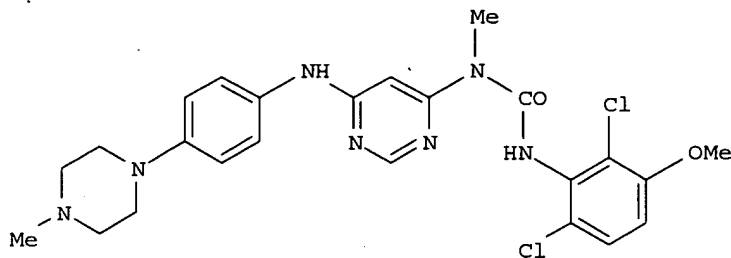
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2006000420	ICM	C07D-0239/48
	ICS	C07D-0409/12; C07D-0401/12; C07D-0405/12; C07D-0403/12; A61K-0031/505; A61K-0031/506; C07D-0251/48; A61P-0035/00
	IPCI	C07D0239-48 [ICM,7]; C07D0409-12 [ICS,7]; C07D0401-12 [ICS,7]; C07D0405-12 [ICS,7]; C07D0403-12 [ICS,7]; A61K0031-505 [ICS,7]; A61K0031-506 [ICS,7]; C07D0251-48 [ICS,7]; A61P0035-00 [ICS,7]
	ECLA	C07D239/48B1; C07D251/48; C07D401/12; C07D403/12; C07D405/12; C07D409/12

GI



I



II

AB The invention relates to pyrimidine urea derivs. (shown as I; variables defined below; e.g. 3-(2,6-dichloro-3-methoxyphenyl)-1-methyl-1-[6-[(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea (II)), to processes for the preparation of these compds., pharmaceutical compns. containing same, the use thereof optionally in combination with ≥ 1 other pharmaceutically active compds. for the therapy of a disease which responds to an inhibition of protein kinase activity, and a method for the treatment of such a disease. Inhibitory activity of some examples of I are included, e.g. N-[3-[3-(6-aminopyrimidin-4-yl)-3-[3-(2-oxopyrrolidin-1-yl)propyl]ureido]-4-methylphenyl]-3-trifluoromethylbenzamide at a concentration of 10 μ M inhibits the following kinases by the percentage shown in brackets: wild-type Abl (99%), c-RAF (99%), CSK (97%), c-SRC (100%), FGFR35 (99%), JNK2 α 2 (93%), lck (100%), MKK6 (88%), p70S6K (81%), ROS (95%), SAPK2 α (99%), SAPK2 β (99%), Tie2 (100%) and TrkB (99%). For I: n = 0-5; X, Y and Z = N or CR5, wherein at least two of X, Y and Z are N; X₁ is O; R₁, R₂, R₃ and R₄, if present, = an organic or inorg. moiety, where the inorg. moiety especially = halo, especially chloro, hydroxy, cyano, azido, nitro; and where the organic moiety is (un)substituted and may be attached via a linker, -L1-, the organic moiety especially = H lower aliphatic, amino, guanidino, hydroxyguanidino, formamidino, isothioureido, et al. and -L1- has 1-5 in-chain atoms (e.g. = C, N, O and S) and optionally = (i) C1-C4 alkyl, such an alkyl group optionally being interrupted and/ or terminated by an -O-, -C(O)- or -NRa- linkage, -O-, -S-, -C(O)-, cyclopropyl (regarded as having two in-chain atoms) and chemical appropriate combinations thereof. R₁ can also = -X5NR7R8, -X5NR7X5NR7R8, -X5NR7X5C(O)OR8, -X5OR7, -X5R7 and -X5S(O)O-2R7 (X₅ is a bond or (un)substituted C1-4alkylene; R₇ =

H, C1-6alkyl, C6-10aryl-C0-4alkyl, C5-10heteroaryl-C0-4alkyl, C3-10cycloalkyl-C0-4alkyl and C3-10heterocycloalkyl-C0-4alkyl; and R8 = H and C1-6alkyl; or R7 and R8 together with the N to which R7 and R8 are both attached form heteroaryl or heterocycloalkyl); wherein R3 can alternatively = H, C1-4alkyl, C6-10aryl-C0-4alkyl, C5-10heteroaryl-C0-4alkyl, C3-10cycloalkyl-C0-4alkyl and C3-10heterocycloalkyl-C0-4alkyl. Each R4 is the same or different and = an organic or inorg. moiety, e.g. halogen, hydroxy, protected hydroxy; one of the R4 can also = -L1-A-R16m (L1 is a linker; m is 0-5; A is a ring; R16, if present, = an organic or inorg. moiety, where the inorg. moiety especially = halo, especially

chloro,

hydroxy, cyano, azido, nitro; and where the organic moiety is (un)substituted and may be attached via a linker, -L2-, the organic moiety being especially = H, lower aliphatic (especially C1-C4 aliphatic), et al.; L1 and L2 each independently = moieties having 1-5 in-chain atoms (e.g. = C, N, O and S) and optionally being = C1-C4 alkyl, such an alkyl group optionally being interrupted and/or terminated by an -O-, -C(O)- or -NRA- linkage, -O-, -S-, -C(O)-, cyclopropyl (regarded as having two in-chain atoms) and chemical appropriate combinations thereof); addnl. details including provisos are given in the claims. Although the methods of preparation are not claimed, preps. and/or characterization data for >200 examples of I are included. For example, II was prepared from 2,6-dichloro-3-methoxyphenyl isocyanate (preparation given) and N-methyl-N'-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidine-4,6-diamine (preparation given).

ST pyrimidine urea prepn kinase inhibitor antiproliferative agent

IT Enzymes, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study) (FGFR35 kinase, inhibitors; preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)

IT Cytotoxic agents

(codrugs; preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)

IT Ureas

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidates; preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)

IT Antitumor agents

Combination chemotherapy

Drug delivery systems

Human

Neoplasm

(preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)

IT Disease, animal

(proliferative; preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)

IT 220127-57-1, Glivec

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(codrug; preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)

IT

872509-57-4P, 3-(2,6-Dichloro-3-methoxyphenyl)-1-methyl-1-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-59-6P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-methyl-1-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-60-9P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-methyl-1-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-61-0P, 1-(2,6-Dichlorophenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-62-1P, 1-(2,6-Dichlorophenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-63-2P, 1-(2-Chloro-6-methylphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-64-3P, 1-(2-Chloro-6-methylphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-65-4P, 1-(3-Methoxyphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-66-5P, 1-(3-Methoxyphenyl)-3-

[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-67-6P, 1-(3,5-Dichlorophenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-68-7P, 1-(3,5-Dichlorophenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-69-8P, 1-(2,5-Dimethoxyphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-70-1P, 1-(2,5-Dimethoxyphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-71-2P, 1-[6-[[4-(4-Methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]-3-(3,4,5-trimethoxyphenyl)urea
872509-72-3P, 1-[6-[[3-(4-Methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]-3-(3,4,5-trimethoxyphenyl)urea 872509-73-4P, 1-(2,4-Dimethoxyphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-74-5P, 1-(2,4-Dimethoxyphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-75-6P, 1-(3,5-Dimethoxyphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-76-7P, 1-(3,5-Dimethoxyphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-77-8P, 1-[3,5-Bis(trifluoromethyl)phenyl]-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-78-9P, 1-[3,5-Bis(trifluoromethyl)phenyl]-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-79-0P, 1-(3,5-Dimethylphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-80-3P, 1-(3,5-Dimethylphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-81-4P, 1-(3-Chloro-4-methoxyphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-82-5P, 1-(3-Chloro-4-methoxyphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-83-6P, 1-(5-Methoxy-2-methylphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-84-7P, 1-(5-Methoxy-2-methylphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-85-8P, 1-(2-Chloro-5-methoxyphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-86-9P, 1-(2-Chloro-5-methoxyphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-87-0P, 1-(3,4-Dimethoxyphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-88-1P, 1-(3,4-Dimethoxyphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-89-2P, 1-(4-Fluoro-3-methoxyphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-90-5P, 1-(4-Fluoro-3-methoxyphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-91-6P, 1-(4,5-Dimethoxy-2-methylphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-92-7P, 1-(4,5-Dimethoxy-2-methylphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-93-8P, 1-(2,6-Dichloro-3-methoxyphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-94-9P, 1-(2,6-Dichloro-3-methoxyphenyl)-3-[6-[[3-[2-(morpholin-4-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]urea 872509-95-0P, 1-(2-Chloro-3,5-dimethoxyphenyl)-3-(6-methylaminopyrimidin-4-yl)urea
872509-96-1P, 1-(2-Chloro-3,5-dimethoxyphenyl)-3-(6-phenylaminopyrimidin-4-yl)urea 872509-97-2P, 1-(2-Chloro-3,5-dimethoxyphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872509-98-3P, 1-(2-Chloro-3,5-dimethoxyphenyl)-3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872509-99-4P, 1-(2-Chloro-3,5-dimethoxyphenyl)-3-[6-[[4-(2-diethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]urea
872510-00-4P, 1-(2-Chloro-3,5-dimethoxyphenyl)-3-[6-[[3-(2-dimethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]urea 872510-01-5P, 1-(2-Chloro-3,5-dimethoxyphenyl)-3-[6-[[4-[2-(morpholin-4-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]urea
872510-03-7P, 1-(2-Chloro-3,5-dimethoxyphenyl)-3-[6-[[3-[2-(morpholin-4-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]urea 872510-05-9P, 3-(2,3-Dimethoxyphenyl)-1-ethyl-1-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872510-06-0P, 3-(3,5-Dimethoxyphenyl)-1-methyl-1-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea
872510-07-1P, 3-(3,5-Dimethoxyphenyl)-1-methyl-1-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-08-2P, 3-(2-Chloro-3,5-

dimethoxyphenyl)-1-methyl-1-(6-phenylaminopyrimidin-4-yl)urea
 872510-09-3P, 3-(2-Chloro-3,5-dimethoxyphenyl)-1-methyl-1-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-10-6P,
 3-(2-Chloro-3,5-dimethoxyphenyl)-1-methyl-1-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-11-7P, 3-(2-Chloro-3,5-dimethoxyphenyl)-1-methyl-1-[6-[[4-[(4-methylpiperazin-1-yl)carbonyl]phenyl]amino]pyrimidin-4-yl]urea 872510-13-9P,
 3-(2-Chloro-3,5-dimethoxyphenyl)-1-[6-[[4-(2-diethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]-1-methylurea 872510-15-1P, 3-(2-Chloro-3,5-dimethoxyphenyl)-1-[6-[[3-(2-dimethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]-1-methylurea 872510-16-2P, 3-(2-Chloro-3,5-dimethoxyphenyl)-1-ethyl-1-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-17-3P, 3-(2-Chloro-3,5-dimethoxyphenyl)-1-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]-1-thiophen-2-ylmethylurea 872510-18-4P, 3-(2-Chloro-3,5-dimethoxyphenyl)-1-[2-(4-methylpiperazin-1-yl)ethyl]-1-(6-phenylaminopyrimidin-4-yl)urea 872510-19-5P,
 3-(2-Chloro-3,5-dimethoxyphenyl)-1-(6-phenylaminopyrimidin-4-yl)-1-[2-(pyridin-2-yl)ethyl]urea 872510-20-8P, 3-(2,6-Dichloro-3-methoxyphenyl)-1-ethyl-1-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-21-9P, 3-(2,6-Dichloro-3-methoxyphenyl)-1-methyl-1-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-22-0P, 3-(2,6-Dichloro-3-methoxyphenyl)-1-methyl-1-[6-[[4-[(4-methylpiperazin-1-yl)carbonyl]phenyl]amino]pyrimidin-4-yl]urea 872510-23-1P, 3-(2,6-Dichloro-3-methoxyphenyl)-1-methyl-1-[6-[[4-[(4-methylpiperazin-1-yl)methyl]phenyl]amino]pyrimidin-4-yl]urea 872510-24-2P, 3-(2,6-Dichloro-3-methoxyphenyl)-1-[(6-methoxypyridin-3-yl)methyl]-1-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-25-3P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-ethyl-1-[6-[[4-[(4-methylpiperazin-1-yl)carbonyl]phenyl]amino]pyrimidin-4-yl]urea 872510-26-4P, 1-(2-Chloro-6-methylphenyl)-3-(6-isopropylaminopyrimidin-4-yl)urea 872510-27-5P, (2,6-Dichlorophenyl)carbamic acid 4-[[6-[3-(2,6-dichlorophenyl)ureido]pyrimidin-4-yl]amino]cyclohexyl ester 872510-28-6P, 1-(6-Isopropylaminopyrimidin-4-yl)-3-(2,4,6-trichlorophenyl)urea 872510-29-7P, 1-(2,6-Dichlorophenyl)-3-(6-isopropylaminopyrimidin-4-yl)urea 872510-30-0P, 1-[6-[[4-[(1-Methylpiperidin-4-yl)methoxy]phenyl]amino]pyrimidin-4-yl]-3-(2,4,6-trichlorophenyl)urea 872510-31-1P, 1-(2-Chloro-6-methylphenyl)-3-[6-[[4-[(1-methylpiperidin-4-yl)methoxy]phenyl]amino]pyrimidin-4-yl]urea 872510-32-2P, 1-(2,6-Dichlorophenyl)-3-[6-[[4-[(1-methylpiperidin-4-yl)methoxy]phenyl]amino]pyrimidin-4-yl]urea 872510-33-3P, 1-(2,5-Dichlorophenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-34-4P, 1-[6-[[4-(4-Methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]-3-(2,4,6-trichlorophenyl)urea 872510-35-5P, 1-[6-[[4-(4-Methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]-3-(2,4,5-trichlorophenyl)urea 872510-36-6P, 1-(3,4-Dichlorophenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-37-7P, 1-(6-Aminopyrimidin-4-yl)-3-(2,3-dichlorophenyl)-1-[4-(4-methylpiperazin-1-yl)phenyl]urea 872510-38-8P, 1-(2,3-Dichlorophenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-39-9P, 1-(5-Chloro-2-methoxyphenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-40-2P, 1-(2-Chloro-6-methylphenyl)-3-[6-[[3-[(1-methylpiperidin-4-yl)methoxy]phenyl]amino]pyrimidin-4-yl]urea 872510-41-3P, 1-(2,6-Dichlorophenyl)-3-[6-[[3-[(1-methylpiperidin-4-yl)methoxy]phenyl]amino]pyrimidin-4-yl]urea 872510-42-4P, 1-[6-[[3-[(1-Methylpiperidin-4-yl)methoxy]phenyl]amino]pyrimidin-4-yl]-3-(2,4,6-trichlorophenyl)urea 872510-43-5P, 1-(2-Chloro-6-methylphenyl)-3-[6-[[4-[(4-methylpiperazin-1-yl)methyl]phenyl]amino]pyrimidin-4-yl]urea 872510-44-6P, 1-(2,6-Dichlorophenyl)-3-[6-[[4-[(4-methylpiperazin-1-yl)methyl]phenyl]amino]pyrimidin-4-yl]urea 872510-45-7P, 1-[6-[[4-[(4-Methylpiperazin-1-yl)methyl]phenyl]amino]pyrimidin-4-yl]-3-(2,4,6-trichlorophenyl)urea 872510-46-8P, 1-[6-[[4-[(4-Methylpiperazin-1-yl)carbonyl]phenyl]amino]pyrimidin-4-yl]-3-(2,4,6-trichlorophenyl)urea 872510-47-9P, 1-[6-[[3-(4-Methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]-3-(2,4,6-trichlorophenyl)urea 872510-48-0P, 1-[6-[[trans-4-[(tert-Butyldimethylsilyl)oxy]cyclohexyl]amino]pyrimidin-4-yl]-3-(2,4,6-

trichlorophenyl)urea 872510-49-1P, 1-[6-[(trans-4-Hydroxycyclohexyl)amino]pyrimidin-4-yl]-3-(2,4,6-trichlorophenyl)urea 872510-50-4P, 1-[6-[(trans-4-[(tert-Butyldimethylsilyl)oxy]cyclohexyl)amino]pyrimidin-4-yl]-3-(2-chloro-6-methylphenyl)urea 872510-51-5P, 1-(2-Chloro-6-methylphenyl)-3-[6-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl]urea 872510-52-6P, 1-[6-[(trans-4-[(tert-Butyldimethylsilyl)oxy]cyclohexyl)amino]pyrimidin-4-yl]-3-(2,6-dichlorophenyl)urea 872510-53-7P, 1-(2,6-Dichlorophenyl)-3-[6-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl]urea 872510-54-8P, 1-(2-Chlorophenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-55-9P, 1-(2-Bromophenyl)-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-56-0P, 1-(6-Aminopyrimidin-4-yl)-3-(2-chlorophenyl)-1-[4-(3-diethylaminopropoxy)phenyl]urea 872510-57-1P, 1-(2,6-Dichlorophenyl)-3-[6-[[4-[2-(morpholin-4-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]urea 872510-58-2P, 1-(2-Bromophenyl)-3-[6-[[4-[2-(morpholin-4-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]urea 872510-59-3P, 1-(2,6-Dichlorophenyl)-3-[6-[[4-[3-(morpholin-4-yl)propoxy]phenyl]amino]pyrimidin-4-yl]urea 872510-60-6P, 1-(2-Bromophenyl)-3-[6-[[4-[3-(morpholin-4-yl)propoxy]phenyl]amino]pyrimidin-4-yl]urea 872510-61-7P, 1-(2,6-Dichlorophenyl)-3-[6-[[4-(2-diethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]urea 872510-62-8P, 1-(2-Bromophenyl)-3-[6-[[4-(2-diethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]urea 872510-63-9P, 1-(2-Chlorophenyl)-3-[6-[[4-(3-diethylaminopropoxy)phenyl]amino]pyrimidin-4-yl]urea 872510-64-0P, 1-(2,6-Dichlorophenyl)-3-[6-[[4-(3-diethylaminopropoxy)phenyl]amino]pyrimidin-4-yl]urea 872510-66-2P, 1-[6-[[4-Diethylaminophenyl]amino]pyrimidin-4-yl]-3-(2,6-difluorophenyl)urea 872510-68-4P, 1-(2,6-Difluorophenyl)-3-[6-[[3-dimethylaminophenyl]amino]pyrimidin-4-yl]urea 872510-70-8P, 1-(2,6-Dichlorophenyl)-3-[6-[[4-diethylaminophenyl]amino]pyrimidin-4-yl]urea 872510-71-9P, 1-(2,6-Dichlorophenyl)-3-[6-[[4-(morpholin-4-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-73-1P, 1-(2,6-Difluorophenyl)-3-[6-[[4-(morpholin-4-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-74-2P, 3-(2,6-Dichlorophenyl)-1-[6-[[4-diethylaminophenyl]amino]pyrimidin-4-yl]-1-methylurea 872510-76-4P, 3-(2,6-Dichlorophenyl)-1-[6-[[4-(1-hydroxy-1-methylethyl)phenyl]amino]pyrimidin-4-yl]-1-methylurea 872510-79-7P, 1-(2,6-Dichlorophenyl)-3-[6-[[6-methoxy-pyridin-3-yl]amino]pyrimidin-4-yl]urea 872510-81-1P, 3-(2,6-Dichlorophenyl)-1-methyl-1-[6-[[3-trifluoromethylphenyl]amino]pyrimidin-4-yl]urea 872510-84-4P, 1-[6-(3-Cyanophenylamino)pyrimidin-4-yl]-3-(2,6-dichlorophenyl)-1-methylurea 872510-88-8P, 1-(2,6-Dichlorophenyl)-3-[6-(4-fluorophenylamino)pyrimidin-4-yl]-1-methylurea 872510-93-5P, 1-[6-(4-Fluorophenylamino)pyrimidin-4-yl]-3-(4-methoxyphenyl)-1-methylurea 872510-95-7P, 3-(2,6-Dichlorophenyl)-1-methyl-1-[6-[[4-(morpholin-4-yl)phenyl]amino]pyrimidin-4-yl]urea 872510-97-9P, 3-(2,6-Dichlorophenyl)-1-[6-(2,4-difluorophenylamino)pyrimidin-4-yl]-1-methylurea 872511-00-7P, 1-(2,6-Dichlorophenyl)-3-[6-[[3-dimethylaminophenyl]amino]pyrimidin-4-yl]urea 872511-01-8P, 3-(2,6-Dichlorophenyl)-1-[6-[[3-dimethylaminophenyl]amino]pyrimidin-4-yl]-1-methylurea 872511-03-0P, 1-[6-(4-Fluorophenylamino)pyrimidin-4-yl]-1-methyl-3-(3-trifluoromethylphenyl)urea 872511-04-1P, 3-(3'-Chlorophenyl)-1-[6-(4-fluorophenylamino)pyrimidin-4-yl]-1-methylurea 872511-05-2P, 3-(2,6-Dichlorophenyl)-1-[6-(4-fluorophenylamino)pyrimidin-4-yl]-1-methylurea 872511-06-3P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-yl]-3-(2,6-dichlorophenyl)-1-methylurea 872511-08-5P, 1-(2-Chlorophenyl)-3-[6-[[4-[3-(morpholin-4-yl)propoxy]phenyl]amino]pyrimidin-4-yl]urea dihydrochloride 872511-10-9P, 1-(2-Chlorophenyl)-3-[6-[[4-(2-diethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]urea 872511-11-0P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-yl]-3-(2,6-dimethylphenyl)-1-methylurea 872511-12-1P, 3-(2-Chlorophenyl)-1-[6-(3-chlorophenylamino)pyrimidin-4-yl]urea 872511-14-3P, 1-(2-Bromophenyl)-3-[6-(3-chlorophenylamino)pyrimidin-4-yl]urea 872511-15-4P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-yl]-3-(2-fluorophenyl)urea 872511-16-5P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-yl]-3-(3-methoxyphenyl)urea 872511-17-6P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-

yl]-3-(2,5-dimethoxyphenyl)urea 872511-18-7P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-yl]-3-(2-trifluoromethylphenyl)urea
 872511-19-8P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-yl]-3-(5-methoxy-2-methylphenyl)urea 872511-20-1P, 1-(3-Chlorophenyl)-3-[6-(3-chlorophenylamino)pyrimidin-4-yl]urea 872511-21-2P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-yl]-3-(3,4,5-trimethoxyphenyl)urea
 872511-22-3P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-yl]-3-(2,6-dichlorophenyl)urea 872511-23-4P, 1-(4-Chlorophenyl)-3-[6-(3-chlorophenylamino)pyrimidin-4-yl]urea 872511-24-5P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-yl]-3-(3,5-dimethoxyphenyl)urea
 872511-25-6P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-yl]-3-(2,6-dimethylphenyl)urea 872511-26-7P, 1-[6-(3-Chlorophenylamino)pyrimidin-4-yl]-3-phenylurea 872511-27-8P, 1-(2-Chlorophenyl)-3-[6-[[4-[2-(morpholin-4-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]urea 872511-28-9P,
 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-ethyl-1-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872511-31-4P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[3-[(dimethylamino)methyl]phenyl]amino]pyrimidin-4-yl]-1-methylurea 872511-34-7P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[4-(4-ethylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]-1-methylurea
 872511-36-9P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-methyl-1-[6-[[4-[3-(4-methylpiperazin-1-yl)propoxy]phenyl]amino]pyrimidin-4-yl]urea
 872511-38-1P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[4-(3-dimethylaminopropyl)phenyl]amino]pyrimidin-4-yl]-1-methylurea
 872511-40-5P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-methyl-1-[6-[[4-[2-(pyrrolidin-1-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]urea 872511-42-7P,
 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[4-[(4-ethylpiperazin-1-yl)methyl]phenyl]amino]pyrimidin-4-yl]-1-methylurea 872511-44-9P,
 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[3-[(4-ethylpiperazin-1-yl)methyl]phenyl]amino]pyrimidin-4-yl]-1-methylurea 872511-47-2P,
 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[3-[(dimethylamino)methyl]phenyl]amino]pyrimidin-4-yl]-1-ethylurea
 872511-49-4P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[4-(2-diethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]-1-methylurea
 872511-51-8P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[2,6-dimethylpyridin-3-yl]amino]pyrimidin-4-yl]-1-methylurea 872511-53-0P,
 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-methyl-1-[6-[[6-trifluoromethylpyridin-3-yl]amino]pyrimidin-4-yl]urea 872511-55-2P,
 1-(2,6-Dichloro-3,5-dimethoxyphenyl)-3-[6-[[4-[2-(pyrrolidin-1-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]urea 872511-57-4P,
 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-ethyl-1-[6-[[4-[2-(pyrrolidin-1-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]urea 872511-59-6P,
 1-(2,6-Dichloro-3,5-dimethoxyphenyl)-3-[6-[[3-[(dimethylamino)methyl]phenyl]amino]pyrimidin-4-yl]urea 872511-61-0P,
 1-(2,6-Dichloro-3,5-dimethoxyphenyl)-3-[6-[[4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]urea 872511-63-2P,
 1-(2,6-Dichloro-3,5-dimethoxyphenyl)-3-[6-[[4-[(dimethylamino)methyl]-3-trifluoromethylphenyl]amino]pyrimidin-4-yl]urea 872511-65-4P,
 1-(2,6-Dichloro-3,5-dimethoxyphenyl)-3-[6-[[4-(4-ethylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872511-67-6P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[3-[(4-isopropylpiperazin-1-yl)methyl]phenyl]amino]pyrimidin-4-yl]-1-methylurea 872511-70-1P,
 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[3-[[2-dimethylaminoethyl](methyl)amino]methyl]phenyl]amino]pyrimidin-4-yl]-1-methylurea 872511-74-5P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[4-(4-isopropylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]-1-methylurea
 872511-76-7P, N-[4-Methyl-3-[3-methyl-3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide
 872511-77-8P, N-[4-Methyl-3-[3-(6-methylaminopyrimidin-4-yl)ureido]phenyl]-3-trifluoromethylbenzamide 872511-78-9P, N-[4-Methyl-3-[3-(6-phenylaminopyrimidin-4-yl)ureido]phenyl]-3-trifluoromethylbenzamide
 872511-79-0P, N-[4-Methyl-3-[3-[6-[[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide
 872511-80-3P, N-[4-Methyl-3-[3-[6-[[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide
 872511-81-4P, N-[3-[3-[6-[[4-(2-Diethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]ureido]-4-methylphenyl]-3-trifluoromethylbenzamide 872511-82-5P,

N-[3-[3-[6-[4-(3-Dimethylaminopropoxy)phenyl]amino]pyrimidin-4-yl]ureido]-4-methylphenyl]-3-trifluoromethylbenzamide 872511-83-6P,
N-[3-[3-[6-[3-(2-Dimethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]ureido]-4-methylphenyl]-3-trifluoromethylbenzamide 872511-84-7P,
N-[4-Methyl-3-[3-[6-[4-(2-(morpholin-4-yl)ethoxy)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide 872511-85-8P,
N-[4-Methyl-3-[3-[6-[3-(2-(morpholin-4-yl)ethoxy)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide 872511-86-9P,
N-[4-Methyl-3-[3-methyl-3-(6-phenylaminopyrimidin-4-yl)ureido]phenyl]-3-trifluoromethylbenzamide 872511-87-0P, N-[3-[3-[6-[3-(2-Dimethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]-3-methylureido]-4-methylphenyl]-3-trifluoromethylbenzamide 872511-88-1P,
N-[3-[3-[6-[4-(2-Diethylaminoethoxy)phenyl]amino]pyrimidin-4-yl]-3-methylureido]-4-methylphenyl]-3-trifluoromethylbenzamide 872511-89-2P,
N-[4-Methyl-3-[3-methyl-3-[6-[4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide 872511-90-5P, N-[4-Methyl-3-[3-methyl-3-[6-[3-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide 872511-91-6P, 4-Methyl-3-[3-methyl-3-[6-[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]ureido]-N-(3-trifluoromethylphenyl)benzamide 872511-92-7P, N-[4-Methyl-3-[3-methyl-3-[6-[4-(4-methylpiperazin-1-yl)carbonyl]phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide 872511-93-8P, N-[4-Methyl-3-[3-methyl-3-[6-[3-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide 872511-94-9P, N-[4-Methyl-3-[3-[2-(4-methylpiperazin-1-yl)ethyl]-3-(6-phenylaminopyrimidin-4-yl)ureido]phenyl]-3-trifluoromethylbenzamide 872511-95-0P, N-[4-Methyl-3-[3-(6-phenylaminopyrimidin-4-yl)-3-[2-(pyridin-2-yl)ethyl]ureido]phenyl]-3-trifluoromethylbenzamide 872511-96-1P, N-[4-Methyl-3-[3-[6-[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]-3-[2-(pyridin-2-yl)ethyl]ureido]phenyl]-3-trifluoromethylbenzamide 872511-97-2P,
N-[3-[3-Ethyl-3-[6-[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]ureido]-4-methylphenyl]-3-trifluoromethylbenzamide 872511-98-3P,
N-[4-Methyl-3-[3-[6-[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]-3-thiophen-2-ylmethylureido]phenyl]-3-trifluoromethylbenzamide 872511-99-4P, N-[3-[3-(6-Aminopyrimidin-4-yl)-3-methylureido]-4-methylphenyl]-4-[(4-methylpiperazin-1-yl)methyl]-3-trifluoromethylbenzamide 872512-05-5P, N-[4-Methyl-3-[3-methyl-3-(6-phenylaminopyrimidin-4-yl)ureido]phenyl]-4-[(4-methylpiperazin-1-yl)methyl]-3-trifluoromethylbenzamide 872512-06-6P, 3-(5-Amino-2-methoxyphenyl)-1-methyl-1-[6-[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872512-07-7P, N-[4-Methoxy-3-[3-methyl-3-[6-[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide 872512-08-8P,
N-[4-Methoxy-3-[3-methyl-3-[6-[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-4-[(4-methylpiperazin-1-yl)methyl]-3-trifluoromethylbenzamide 872512-09-9P, N-[3-[3-(6-Aminopyrimidin-4-yl)-3-methylureido]-5-methoxyphenyl]-4-[(4-methylpiperazin-1-yl)methyl]-3-trifluoromethylbenzamide 872512-10-2P,
N-[3-Methoxy-5-[3-methyl-3-(6-phenylaminopyrimidin-4-yl)ureido]phenyl]-4-[(4-methylpiperazin-1-yl)methyl]-3-trifluoromethylbenzamide 872512-11-3P, N-[3-Methoxy-5-[3-methyl-3-[6-[4-(4-methylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-4-methyl-3-trifluoromethylbenzamide 872512-12-4P, N-[3-[3-(6-Acetylaminopyrimidin-4-yl)-3-methylureido]-4-methylphenyl]-4-[(4-methylpiperazin-1-yl)methyl]-3-trifluoromethylbenzamide 872512-13-5P, [6-[1-Methyl-3-[2-methyl-5-[4-[(4-methylpiperazin-1-yl)methyl]-3-trifluoromethylbenzoylamino]phenyl]ureido]pyrimidin-4-yl]carbamic acid methyl ester 872512-14-6P, [6-[1-Methyl-3-[2-methyl-5-[4-[(4-methylpiperazin-1-yl)methyl]-3-trifluoromethylphenyl]carbamoyl]phenyl]ureido]pyrimidin-4-yl]carbamic acid methyl ester 872512-15-7P, 3-[3-(6-Acetylaminopyrimidin-4-yl)-3-methylureido]-4-methyl-N-[4-[(4-methylpiperazin-1-yl)methyl]-3-trifluoromethylphenyl]benzamide 872512-16-8P, 3-[3-(6-Aminopyrimidin-4-yl)-3-methylureido]-4-methyl-N-[4-[(4-methylpiperazin-1-yl)methyl]-3-trifluoromethylphenyl]benzamide 872512-17-9P, N-[4-Methyl-3-[3-methyl-3-

[6-[[[tetrahydrofuran-2-yl)methyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide 872512-22-6P, N-[3-[3-[6-[(Benzodioxol-5-yl)amino]pyrimidin-4-yl]-3-methylureido]-4-methylphenyl]-3-trifluoromethylbenzamide 872512-23-7P, N-[3-[3-[6-[(3-Dimethylaminophenyl)amino]pyrimidin-4-yl]-3-methylureido]-4-methylphenyl]-3-trifluoromethylbenzamide 872512-24-8P, N-[3-[3-[6-[(3-Acetylaminophenyl)amino]pyrimidin-4-yl]-3-methylureido]-4-methylphenyl]-3-trifluoromethylbenzamide 872512-25-9P, N-[4-Methyl-3-[3-methyl-3-[6-[[4-(morpholin-4-yl)phenyl]amino]pyrimidin-4-yl]ureido]phenyl]-3-trifluoromethylbenzamide 872512-27-1P, N-[3-[3-(6-Aminopyrimidin-4-yl)-3-[2-(morpholin-4-yl)ethyl]ureido]-4-methylphenyl]-3-trifluoromethylbenzamide 872512-28-2P, N-[3-[3-(6-Aminopyrimidin-4-yl)-3-[3-(2-oxopyrrolidin-1-yl)propyl]ureido]-4-methylphenyl]-3-trifluoromethylbenzamide 872512-29-3P 872512-30-6P 872512-31-7P 872512-32-8P 872512-33-9P 872512-34-0P 872512-35-1P 872512-36-2P 872512-37-3P 872512-38-4P 872512-39-5P 872512-40-8P 872512-41-9P 872512-42-0P 872512-43-1P 872512-44-2P 872512-45-3P 872512-46-4P 872512-47-5P 872512-48-6P 872512-49-7P 872512-50-0P 872512-51-1P 872512-52-2P 872512-53-3P 872512-54-4P 872512-55-5P 872512-56-6P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)

IT 872512-57-7P 872512-58-8P 872512-59-9P 872512-60-2P 872512-61-3P 872512-62-4P 872512-63-5P 872512-64-6P 872512-66-8P 872512-68-0P 872512-69-1P 872512-70-4P 872512-71-5P 872512-72-6P 872512-73-7P 872512-74-8P 872512-75-9P 872512-76-0P 872512-77-1P 872512-78-2P 872512-79-3P, 1-(6-Aminopyrimidin-4-yl)-1-[2-(morpholin-4-yl)ethyl]-3-(2,4-dimethoxyphenyl)urea 872512-81-7P, 1-(6-Aminopyrimidin-4-yl)-1-[2-(morpholin-4-yl)ethyl]-3-(2,5-dimethoxyphenyl)urea 872512-82-8P, 1-(6-Aminopyrimidin-4-yl)-1-[2-(morpholin-4-yl)ethyl]-3-(3,4-dimethoxyphenyl)urea 872512-83-9P, 1-(6-Aminopyrimidin-4-yl)-1-[2-(morpholin-4-yl)ethyl]-3-(3,5-dimethoxyphenyl)urea 872512-84-0P, 1-(6-Aminopyrimidin-4-yl)-1-[2-(morpholin-4-yl)ethyl]-3-[3,5-bis(trifluoromethyl)phenyl]urea 872512-85-1P, 1-(6-Aminopyrimidin-4-yl)-1-[2-(morpholin-4-yl)ethyl]-3-[3,5-bis(trifluoromethyl)phenyl]thiourea 872512-86-2P, 1-(2,6-Dichloro-3,5-dimethoxyphenyl)-3-[6-[[4-(4-isopropylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]urea 872512-88-4P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-methyl-1-[6-[[4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]urea 872512-90-8P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[4-[(dimethylamino)methyl]-3-trifluoromethylphenyl]amino]pyrimidin-4-yl]-1-methylurea 872512-93-1P, 1-(2,6-Dichloro-3,5-dimethoxyphenyl)-3-[6-[[3-[[1-methylpiperidin-4-yl]oxy]phenyl]amino]pyrimidin-4-yl]urea 872512-96-4P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-methyl-1-[6-[[3-[[1-methylpiperidin-4-yl]oxy]phenyl]amino]pyrimidin-4-yl]urea 872512-98-6P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[3-[(diethylamino)methyl]phenyl]amino]pyrimidin-4-yl]-1-methylurea 872513-00-3P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-methyl-1-[4-[[4-(4-methylpiperazin-1-yl)phenyl]amino]-[1,3,5]triazin-2-yl]urea 872513-03-6P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-methyl-1-[4-[[4-(4-ethylpiperazin-1-yl)phenyl]amino]-[1,3,5]triazin-2-yl]urea 872513-05-8P, 3-(4-Fluoro-3-trifluoromethylphenyl)-1-methyl-1-[4-[[4-(4-ethylpiperazin-1-yl)phenyl]amino]-[1,3,5]triazin-2-yl]urea 872513-06-9P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-methyl-1-[4-[[4-(4-isopropylpiperazin-1-yl)phenyl]amino]-[1,3,5]triazin-2-yl]urea 872513-08-1P, 3-(2,6-Dichloro-3-trifluoromethylphenyl)-1-[6-[[4-(4-ethylpiperazin-1-yl)phenyl]amino]pyrimidin-4-yl]-1-methylurea 872513-09-2P, 1-(2,6-Dichloro-3,5-dimethoxyphenyl)-3-[6-[[4-[[1-methylpiperidin-4-yl]oxy]phenyl]amino]pyrimidin-4-yl]urea 872513-10-5P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-methyl-1-[6-[[4-[[1-methylpiperidin-4-yl]oxy]phenyl]amino]pyrimidin-4-yl]urea 872513-11-6P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-ethyl-1-[6-[[4-[[1-methylpiperidin-4-yl]oxy]phenyl]amino]pyrimidin-4-yl]urea 872513-12-7P, 1-(2,6-Dichloro-3,5-dimethoxyphenyl)-3-[6-[[4-[[4-ethylpiperazin-1-

yl)methyl]-3-trifluoromethylphenyl]amino]pyrimidin-4-yl]urea
872513-13-8P, 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-[6-[[4-[(4-ethylpiperazin-1-yl)methyl]-3-trifluoromethylphenyl]amino]pyrimidin-4-yl]-1-methylurea

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)

IT 79079-06-4, HER1 kinase 80449-02-1, Tyrosine kinase 90698-26-3, p70S6K Kinase 98037-52-6, Abl kinase 114051-78-4 137632-06-5, Protein kinase CSK 137632-09-8, HER2 kinase 138238-67-2, Bcr-Abl kinase 139691-76-2, RAF kinase 144114-11-4, ROS kinase 144697-17-6, c-SRC kinase 146279-92-7, Ret kinase 148047-29-4, Tie2 kinase 149146-03-2, FGFR3 tyrosine kinase 149146-91-8, TrkB kinase 150027-15-9, FGFR1 tyrosine kinase 150316-06-6, FGFR2 tyrosine kinase 150977-45-0, KDR kinase 153570-69-5, FGFR4 tyrosine kinase 165245-96-5, Protein kinase SAPK2a 178303-46-3, Protein kinase BMX 179800-23-8, Protein kinase SAPK2b 194739-73-6, MKK6 kinase 289898-51-7, JNK1 kinase 289899-93-0, JNK2 kinase 372092-80-3, Protein kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(inhibitors; preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)

IT 101463-26-7, PDGFR kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(isoform β , inhibitors; preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)

IT 93-05-0, 4-Amino-N,N-diethylaniline 98-16-8, 3-Aminobenzotrifluoride 99-92-3 100-14-1, 4-Nitrobenzyl chloride 102-28-3, N-(3-Aminophenyl)acetamide 103-71-9, Phenyl isocyanate, reactions 104-12-1, 4-Chlorophenyl isocyanate 106-52-5, 4-Hydroxy-1-methylpiperidine 108-42-9, 3-Chloroaniline 108-44-1, 3-Methylaniline, reactions 109-01-3, N-Methylpiperazine 109-89-7, Diethylamine, reactions 119-32-4, 4-Methyl-3-nitroaniline 123-30-8, 4-Aminophenol 142-25-6, N,N,N'-Trimethylethylenediamine 329-01-1, 3-Trifluoromethylphenyl isocyanate 367-25-9, 2,4-Difluoroaniline 371-40-4, 4-Fluoroaniline 402-67-5, 3-Fluoronitrobenzene 586-78-7, 1-Bromo-4-nitrobenzene 608-31-1, 2,6-Dichloroaniline 619-23-8, 3-Nitrobenzyl chloride 869-24-9 1016-19-9, 3,4,5-Trimethoxyphenyl isocyanate 1193-21-1, 4,6-Dichloropyrimidine 1592-00-3, 2-Bromophenyl isocyanate 2038-03-1, [2-(Morpholin-4-yl)ethyl]amine 2237-30-1, 3-Aminobenzonitrile 2251-65-2, 3-Trifluoromethylbenzoyl chloride 2524-67-6, 4-Morpholinoaniline 2831-66-5, 2,4-Dichloro-[1,3,5]triazine 2836-04-6, N,N-Dimethyl-m-phenylenediamine 2909-38-8, 3-Chlorophenyl isocyanate 3320-83-0, 2-Chlorophenyl isocyanate 3430-33-9, 3-Amino-2,6-dimethylpyridine 4795-29-3D, [(Tetrahydrofuran-2-yl)methyl]amine, Pal-resin bearing 5305-59-9, (6-Chloropyrimidin-4-yl)amine 5308-25-8, 1-Ethylpiperazine 5416-93-3, 4-Methoxyphenyl isocyanate 6628-77-9, 5-Amino-2-methoxypyridine 7223-38-3, 3-Dimethylamino-1-propyne 7250-67-1, 1-(2-Chloroethyl)pyrrolidine hydrochloride 7663-77-6, 1-(3-Aminopropyl)pyrrolidin-2-one 13471-68-6, 2-Methyl-5-nitrophenyl isocyanate 14268-66-7D, (Benzodioxol-5-yl)amine, Pal-resin bearing 16153-81-4, 4-(4-Methylpiperazin-1-yl)aniline 16744-98-2, 2-Fluorophenyl isocyanate 18908-07-1, 3-Methoxyphenyl isocyanate 27958-77-6, [3-[(Dimethylamino)methyl]phenyl]amine 28556-81-2, 2,6-Dimethylphenyl isocyanate 38948-28-6, [4-[2-(4-Methylpiperazin-1-yl)ethoxy]phenyl]amine 39920-37-1, 2,6-Dichlorophenyl isocyanate 50868-72-9, 5-Methoxy-2-methylaniline 52481-41-1, [4-[2-(Morpholin-4-yl)ethoxy]phenyl]amine 54132-76-2, 3,5-Dimethoxyphenyl isocyanate 56309-62-7, 2,5-Dimethoxyphenyl isocyanate 61693-43-4, 2,4-Dichloro-3-aminophenol hydrochloride 65295-69-4, 2,6-Difluorophenyl isocyanate 65934-74-9, 5-Amino-2-methylbenzotrifluoride 77270-74-7, 1-(3-Chloropropyl)-4-methylpiperazine hydrochloride 79257-61-7, N-(3,5-Dimethoxyphenyl)acetamide 100800-40-6, [4-[3-(Morpholin-4-

yl)propoxy]phenyl]amine 106877-33-2, 3-Amino-6-(trifluoromethyl)pyridine
 124623-36-5, N,N-Dimethylbenzene-1,3-diamine monohydrochloride
 139057-86-6, 4-Fluoro-3-trifluoromethylphenyl isocyanate 203915-49-5,
 2,4-Dichloro-3-nitrobenzotrifluoride 261952-01-6, 4-Methyl-3-
 trifluoromethylbenzoic acid 872510-94-6, N-(4-Fluorophenyl)-N'-
 methylpyrimidine-4,6-diamine 872512-01-1, 4-[(4-Methylpiperazin-1-
 yl)methyl]-2-trifluoromethylbenzoic acid 872512-92-0,
 N-[3-[(2-Dimethylaminoethyl)(methyl)amino]methyl]phenyl]pyrimidine-4,6-
 diamine

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of pyrimidine urea derivs. as kinase inhibitors for use against
 proliferative diseases)

IT 6656-72-0P, 2,6-Dichloro-3-trifluoromethylaniline 27958-92-5P,
 Diethyl(3-nitrobenzyl)amine 27958-97-0P, [3-
 [(Diethylamino)methyl]phenyl]amine 30069-31-9P, N-(3-Amino-4-
 methylphenyl)-3-trifluoromethylbenzamide 38519-63-0P,
 4-(2-Diethylaminoethoxy)phenylamine 42817-60-7P, 4-(3-
 Dimethylaminopropyl)phenylamine 50609-01-3P, [4-[2-(Pyrrolidin-1-
 yl)ethoxy]phenyl]amine 55285-43-3P, 2,6-Dichloro-3-methoxyaniline
 65766-32-7P, (6-Chloropyrimidin-4-yl)methylamine 104097-50-9P,
 Dimethyl[3-(4-nitrophenyl)prop-2-ynyl]amine 115619-00-6P,
 1-Ethyl-4-(4-nitrophenyl)piperazine 115619-01-7P, 4-(4-Ethylpiperazin-1-
 yl)aniline 220822-26-4P, [4-[3-(4-Methylpiperazin-1-
 yl)propoxy]phenyl]amine 221876-21-7P, N-(4-Methyl-3-nitrophenyl)-3-
 trifluoromethylbenzamide 354112-08-6P 414880-35-6P,
 1-Ethyl-4-(4-nitrobenzyl)piperazine 414890-12-3P, 1-Ethyl-4-(3-
 nitrobenzyl)piperazine 428834-99-5P, 1-Isopropyl-4-(3-
 nitrobenzyl)piperazine 443914-85-0P, 1-Isopropyl-4-(4-
 nitrophenyl)piperazine 443914-86-1P, 4-(4-Isopropylpiperazin-1-
 yl)phenylamine 573704-48-0P, N-(2-Chloro-3,5-dimethoxyphenyl)acetamide
 611225-86-6P, [4-[(4-Ethylpiperazin-1-yl)methyl]phenyl]amine
 630125-84-7P, N-(4-Bromomethyl-3-trifluoromethylphenyl)-2,2,2-
 trifluoroacetamide 630125-85-8P, N-(4-Methyl-3-trifluoromethylphenyl)-
 2,2,2-trifluoroacetamide 790667-66-2P, [3-[(1-Methylpiperidin-4-
 yl)oxyl]phenyl]amine 853297-25-3P, [4-[(Dimethylamino)methyl]-3-
 trifluoromethylphenyl]amine 859026-99-6P, Ethyl 4-methyl-3-
 trifluoromethylbenzoate 859027-00-2P, Ethyl 4-[(4-methylpiperazin-1-
 yl)methyl]-3-trifluoromethylbenzoate 859027-01-3P, Ethyl
 4-bromomethyl-3-trifluoromethylbenzoate 859282-11-4P,
 4-[(4-Methylpiperazin-1-yl)methyl]-3-trifluoromethylbenzoic acid
 872509-55-2P, 2,6-Dichloro-3-methoxyphenyl isocyanate 872509-56-3P,
 2,6-Dichloro-3,5-dimethoxyaniline 872509-58-5P, N-Methyl-N'-[4-(4-
 methylpiperazin-1-yl)phenyl]pyrimidine-4,6-diamine 872510-67-3P,
 N-(4-Diethylaminophenyl)pyrimidine-4,6-diamine 872510-69-5P,
 N-(3-Dimethylaminophenyl)pyrimidine-4,6-diamine 872510-72-0P,
 N-[4-(Morpholin-4-yl)phenyl]pyrimidine-4,6-diamine 872510-75-3P,
 N-(4-Diethylaminophenyl)-N'-methylpyrimidine-4,6-diamine 872510-77-5P,
 1-[4-[(6-Methylaminopyrimidin-4-yl)amino]phenyl]ethanone 872510-78-6P,
 1-[6-(4-Acetylphenylamino)pyrimidin-4-yl]-3-(2,6-dichlorophenyl)-1-
 methylurea 872510-80-0P, N-(6-Methoxypyridin-3-yl)pyrimidine-4,6-diamine
 872510-82-2P, (6-Chloropyrimidin-4-yl)(3-trifluoromethylphenyl)amine
 872510-83-3P, N-Methyl-N'-(3-trifluoromethylphenyl)pyrimidine-4,6-diamine
 872510-85-5P, 3-[(6-Methylaminopyrimidin-4-yl)amino]benzonitrile
 872510-91-3P, N-(4-Fluorophenyl)pyrimidine-4,6-diamine 872510-96-8P,
 N-Methyl-N'-[4-(morpholin-4-yl)phenyl]pyrimidine-4,6-diamine
 872510-99-1P, N-(2,4-Difluorophenyl)-N'-methylpyrimidine-4,6-diamine
 872511-02-9P, N-(3-Dimethylaminophenyl)-N'-methylpyrimidine-4,6-diamine
 872511-07-4P, N-(3-Chlorophenyl)-N'-methylpyrimidine-4,6-diamine
 872511-09-6P, 1-(2-Chlorophenyl)-3-(6-chloropyrimidin-4-yl)urea
 872511-13-2P, N-(3-Chlorophenyl)pyrimidine-4,6-diamine 872511-29-0P,
 N-Ethyl-N'-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidine-4,6-diamine
 872511-30-3P, N-(6-Chloropyrimidin-4-yl)ethylamine 872511-32-5P,
 2,6-Dichloro-3,5-dimethoxyphenyl isocyanate 872511-33-6P,
 N-[3-[(Dimethylamino)methyl]phenyl]-N'-methylpyrimidine-4,6-diamine
 872511-35-8P, N-[4-(4-Ethylpiperazin-1-yl)phenyl]-N'-methylpyrimidine-4,6-
 diamine 872511-37-0P, N-Methyl-N'-[4-[3-(4-methylpiperazin-1-

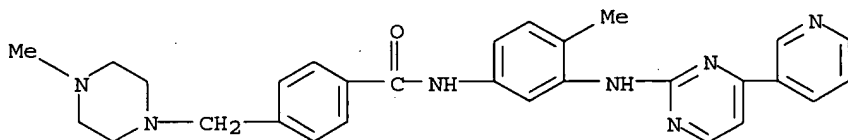
yl)propoxy]phenyl]pyrimidine-4,6-diamine 872511-39-2P,
 N-[4-(3-Dimethylaminopropyl)phenyl]-N'-methylpyrimidine-4,6-diamine
 872511-41-6P, N-Methyl-N'-[4-[2-(pyrrolidin-1-yl)ethoxy]phenyl]pyrimidine-
 4,6-diamine 872511-43-8P, N-[4-[(4-Ethylpiperazin-1-yl)methyl]phenyl]-N'-
 methylpyrimidine-4,6-diamine 872511-45-0P, N-[3-[(4-Ethylpiperazin-1-
 yl)methyl]phenyl]-N'-methylpyrimidine-4,6-diamine 872511-46-1P,
 [3-[(4-Ethylpiperazin-1-yl)methyl]phenyl]amine 872511-48-3P,
 N-[3-[(Dimethylamino)methyl]phenyl]-N'-ethylpyrimidine-4,6-diamine
 872511-50-7P, N-[4-(2-Diethylaminoethoxy)phenyl]-N'-methylpyrimidine-4,6-
 diamine 872511-52-9P, N-(2,6-Dimethylpyridin-3-yl)-N'-methylpyrimidine-
 4,6-diamine 872511-54-1P, N-Methyl-N'-(6-trifluoromethylpyridin-3-
 yl)pyrimidine-4,6-diamine 872511-56-3P, N-[4-[2-(Pyrrolidin-1-
 yl)ethoxy]phenyl]pyrimidine-4,6-diamine 872511-58-5P,
 N-Ethyl-N'-[4-[2-(pyrrolidin-1-yl)ethoxy]phenyl]pyrimidine-4,6-diamine
 872511-60-9P, N-[3-[(Dimethylamino)methyl]phenyl]pyrimidine-4,6-diamine
 872511-62-1P, N-[4-[2-(4-Methylpiperazin-1-yl)ethoxy]phenyl]pyrimidine-4,6-
 diamine 872511-64-3P, N-[4-[(Dimethylamino)methyl]-3-
 trifluoromethylphenyl]pyrimidine-4,6-diamine 872511-66-5P,
 N-[4-(4-Ethylpiperazin-1-yl)phenyl]pyrimidine-4,6-diamine 872511-68-7P,,
 N-[3-[(4-Isopropylpiperazin-1-yl)methyl]phenyl]-N'-methylpyrimidine-4,6-
 diamine 872511-69-8P, [3-[(4-Isopropylpiperazin-1-yl)methyl]phenyl]amine
 872511-71-2P, N-[3-[(2-Dimethylaminoethyl)(methyl)amino]methyl]phenyl]-N'-
 methylpyrimidine-4,6-diamine 872511-72-3P, N-(3-Aminobenzyl)-N,N',N'-
 trimethylethane-1,2-diamine 872511-73-4P, N,N,N'-Trimethyl-N'-(3-
 nitrobenzyl)ethane-1,2-diamine 872511-75-6P, N-[4-(4-Isopropylpiperazin-
 1-yl)phenyl]-N'-methylpyrimidine-4,6-diamine 872512-00-0P, tert-Butyl
 [6-[1-Methyl-3-[2-methyl-5-[4-[(4-methylpiperazin-1-yl)methyl]-3-
 trifluoromethylbenzoylamino]phenyl]ureido]pyrimidin-4-yl]carbamate
 872512-02-2P, tert-Butyl [6-[3-(5-Amino-2-methylphenyl)-1-
 methylureido]pyrimidin-4-yl]carbamate 872512-03-3P, tert-Butyl
 [6-[3-(2-methyl-5-nitrophenyl)-1-methylureido]pyrimidin-4-yl]carbamate
 872512-04-4P, tert-Butyl (6-Methylaminopyrimidin-4-yl)carbamate
 872512-18-0DP, (6-Chloropyrimidin-4-yl)[(tetrahydrofuran-2-
 yl)methyl]amine, Pal-resin bearing 872512-19-1DP, N-Methyl-N'-
 [(tetrahydrofuran-2-yl)methyl]pyrimidine-4,6-diamine, Pal-resin bearing
 872512-20-4DP, 1-Methyl-3-(2-methyl-5-nitrophenyl)-1-[6-[[[(tetrahydrofuran-
 2-yl)methyl]amino]pyrimidin-4-yl]urea, Pal-resin bearing 872512-21-5DP,
 3-(5-Amino-2-methylphenyl)-1-methyl-1-[6-[[[(tetrahydrofuran-2-
 yl)methyl]amino]pyrimidin-4-yl]urea, Pal-resin bearing 872512-26-0P,
 N-[3-[3-(6-Chloropyrimidin-4-yl)-3-methylureido]-4-methylphenyl]-3-
 trifluoromethylbenzamide 872512-87-3P, N-[4-(4-Isopropylpiperazin-1-
 yl)phenyl]pyrimidine-4,6-diamine 872512-89-5P, N-Methyl-N'-[4-[2-(4-
 methylpiperazin-1-yl)ethoxy]phenyl]pyrimidine-4,6-diamine 872512-91-9P,
 N-[4-[(Dimethylamino)methyl]-3-trifluoromethylphenyl]-N'-methylpyrimidine-
 4,6-diamine 872512-94-2P, N-[3-[(1-Methylpiperidin-4-
 yl)oxy]phenyl]pyrimidine-4,6-diamine 872512-95-3P, 1-Methyl-4-(3-
 nitrophenoxy)piperidine 872512-97-5P, N-Methyl-N'-[3-[(1-methylpiperidin-
 4-yl)oxy]phenyl]pyrimidine-4,6-diamine 872512-99-7P,
 N-[3-[(Diethylamino)methyl]phenyl]-N'-methylpyrimidine-4,6-diamine
 872513-01-4P, N-Methyl-N'-[4-(4-methylpiperazin-1-
 yl)phenyl][1,3,5]triazine-2,4-diamine 872513-02-5P, (4-Chloro-
 [1,3,5]triazin-2-yl)methylamine 872513-04-7P, N-Methyl-N'-[4-(4-
 ethylpiperazin-1-yl)phenyl][1,3,5]triazine-2,4-diamine 872513-07-0P,
 N-Methyl-N'-[4-(4-isopropylpiperazin-1-yl)phenyl][1,3,5]triazine-2,4-
 diamine
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (preparation of pyrimidine urea derivs. as kinase inhibitors for use against
 proliferative diseases)

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD

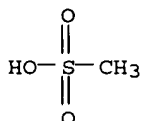
RE

- (1) Boyle; US2004014765 A1 2004 HCAPLUS
- (2) Desai, K; JOURNAL OF THE INDIAN CHEMICAL SOCIETY 1987, V64, P773 HCAPLUS
- (3) Desai, K; JOURNAL OF THE INDIAN CHEMICAL SOCIETY 1994, V71, P151 HCAPLUS
- (4) Hurst, D; AUSTRALIAN JOURNAL OF CHEMISTRY 1988, V41, P1221 HCAPLUS
- (5) Irm Llc; WO2004058713 A 2004 HCAPLUS

(6) Keegan; US2003069284 A1 2003 HCAPLUS
 (7) Kelarev, V; CHEMISTRY OF HETEROCYCLIC COMPOUNDS 1987; V23, P298
 (8) Li; US2004034038 A1 2004
 (9) Modi, B; JOURNAL OF THE INDIAN CHEMICAL SOCIETY 1994, V71, P697 HCAPLUS
 (10) Novartis; WO--03099771 A 2003 HCAPLUS
 (11) Novartis Pharma; WO2005051366 A 2005 HCAPLUS
 (12) Overberger, C; JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 1954, V76, P93 HCAPLUS
 (13) Traverso, J; JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY 1962, V5, P808 HCAPLUS
 IT 220127-57-1, Glivec
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (codrug; preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)
 RN 220127-57-1 HCAPLUS
 CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)
 CM 1
 CRN 152459-95-5
 CMF C29 H31 N7 O



CM 2
 CRN 75-75-2
 CMF C H4 O3 S



IT 146279-92-7, Ret kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (inhibitors; preparation of pyrimidine urea derivs. as kinase inhibitors for use against proliferative diseases)
 RN 146279-92-7 HCAPLUS
 CN Kinase (phosphorylating), gene ret protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L44 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
 AN 2005:570817 HCAPLUS
 DN 143:90995
 ED Entered STN: 01 Jul 2005
 TI Compositions using CDK4 inhibitors for the treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases
 IN Briesewitz, Roger
 PA Theravance, Inc., USA
 SO PCT Int. Appl., 44 pp.
 CODEN: PIXXD2

DT Patent
 LA English
 IC ICM A61K-0038/00
 CC 1-6 (Pharmacology)
 Section cross-reference(s): 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO2005058341	A2	20050630	2004WO-US41333	20041209
	WO2005058341	A3	20051208		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, US			
	RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	US2005171182	A1	20050804	2004US-0008746	20041209
PRAI	2003US-528617P	P	20031211		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2005058341	ICM	A61K-0038/00
	IPCI	A61K0038-00 [ICM,7]; A61P0035-02 [ICS,7]
	IPCR	A61K0031-00 [I,A]; A61K0031-00 [I,C]
US2005171182	IPCI	A61K0031-407 [ICM,7]
	IPCR	A61K0031-407 [I,A]; A61K0031-407 [I,C]
	NCL	514/410.000

AB Uses are provided of a CDK4 inhibitor in the manufacture of a medicament for treating a subject suffering from a cellular proliferative disease characterized by the presence of a mutant receptor tyrosine kinase. The CDK4 inhibitor is for administration either alone or in combination with at least one of an inhibitor of the mutant receptor tyrosine kinase and an MEK inhibitor. Also provided are compns., including pharmaceutical formulations and kits thereof, comprising the above inhibitors.

ST CDK4 inhibitor proliferative disease treatment mutant receptor tyrosine kinase; MEK inhibitor CDK4 inhibitor proliferative disease treatment

IT Cyclins

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (A; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Cyclins

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (B; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Chimeric gene, animal

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (BCR-ABL; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Animal cell line

(BV173; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Antitumor agents

Combination chemotherapy
 Drug delivery systems
 Drug interactions
 Human
 Leukemia

Mutation

Signal transduction, biological

(CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Interleukin 3

RL: PAC (Pharmacological activity); BIOL (Biological study)

(CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Cyclins

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(D1; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Cyclins

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(D2; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Cyclins

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(D3; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Cyclins

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(D; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Animal cell line

(EOL-1; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Animal cell line

(K562; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Animal cell line

(MV4-11; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Animal cell line

(THP-1; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Animal cell line

(U937; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Leukemia

(acute myeloid; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Leukemia

(chronic myelocytic; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Leukemia

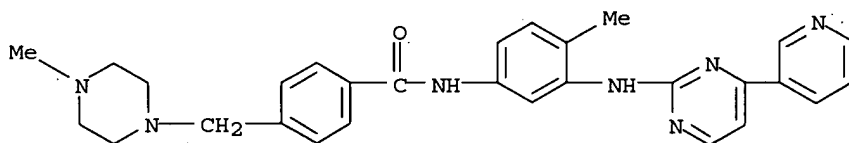
(myelogenous; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(p15; CDK4 inhibitors, alone or in combination with other agents, for treatment of mutant receptor tyrosine kinase-driven cellular proliferative diseases)

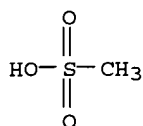
proliferative diseases)
IT Cyclin dependent kinase inhibitors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p16INK4A; CDK4 inhibitors, alone or in combination with other agents,
for treatment of mutant receptor tyrosine kinase-driven cellular
proliferative diseases)
IT Disease, animal
(proliferative; CDK4 inhibitors, alone or in combination with other
agents, for treatment of mutant receptor tyrosine kinase-driven
cellular proliferative diseases)
IT Neoplasm
(solid; CDK4 inhibitors, alone or in combination with other agents, for
treatment of mutant receptor tyrosine kinase-driven cellular
proliferative diseases)
IT 79079-06-4, EGF receptor tyrosine kinase 101463-26-7, Platelet-derived
growth factor receptor tyrosine kinase 136396-12-8, Platelet-derived
growth factor receptor β tyrosine kinase 142805-58-1, MEK
146279-92-7, Ret receptor tyrosine kinase
147014-97-9, CDK4 kinase 147230-71-5, Flt3 kinase 149146-03-2,
Fibroblast growth factor receptor 3 tyrosine kinase 150027-15-9,
Fibroblast growth factor receptor 1 tyrosine kinase 150027-21-7,
Platelet-derived growth factor receptor α tyrosine kinase
166433-56-3, Alk receptor tyrosine kinase 340830-03-7, Receptor tyrosine
kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CDK4 inhibitors, alone or in combination with other agents, for
treatment of mutant receptor tyrosine kinase-driven cellular
proliferative diseases)
IT 83869-56-1, GM-CSF
RL: PAC (Pharmacological activity); BIOL (Biological study)
(CDK4 inhibitors, alone or in combination with other agents, for
treatment of mutant receptor tyrosine kinase-driven cellular
proliferative diseases)
IT 109511-58-2, U0126 118458-54-1, Arcyriaflavin A 220127-57-1,
Imatinib mesylate 560071-94-5, THRX-165724
RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)
(CDK4 inhibitors, alone or in combination with other agents, for
treatment of mutant receptor tyrosine kinase-driven cellular
proliferative diseases)
IT 146279-92-7, Ret receptor tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CDK4 inhibitors, alone or in combination with other agents, for
treatment of mutant receptor tyrosine kinase-driven cellular
proliferative diseases)
RN 146279-92-7 HCAPLUS
CN Kinase (phosphorylating), gene ret protein (9CI) (CA INDEX NAME)
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT 220127-57-1, Imatinib mesylate
RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)
(CDK4 inhibitors, alone or in combination with other agents, for
treatment of mutant receptor tyrosine kinase-driven cellular
proliferative diseases)
RN 220127-57-1 HCAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-
pyridinyl)-2-pyrimidinyl]amino]phenyl]-, monomethanesulfonate (9CI) (CA
INDEX NAME)
CM 1
CRN 152459-95-5
CMF C29 H31 N7 O



CM 2

CRN 75-75-2

CMF C H4 O3 S



L44 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
 AN 2005:128480 HCAPLUS
 DN 142:423220
 ED Entered STN: 15 Feb 2005
 TI Dual Inhibition of RET and FGFR4 Restrains Medullary Thyroid Cancer Cell Growth
 AU Ezzat, Shereen; Huang, Ping; Dackiw, Alan; Asa, Sylvia L.
 CS Department of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, ON, Can.
 SO Clinical Cancer Research (2005), 11(3), 1336-1341
 CODEN: CCRE4; ISSN: 1078-0432
 PB American Association for Cancer Research
 DT Journal
 LA English
 CC 1-6 (Pharmacology)
 AB Medullary thyroid cancer is frequently an aggressive form of carcinoma for which there are currently no effective forms of systemic therapy. These carcinomas arise as a result of activating mutations in the RET proto-oncogene transmembrane tyrosine kinase receptor. We, therefore, examined the potential efficacy of the tyrosine kinase inhibitor STI571 on the growth of human TT medullary cancer cells in vitro and in xenografted severe combined immunodeficiency mice. Treatment with STI571 resulted in inhibition of RET phosphorylation, cell proliferation, tumor growth and invasiveness. Based on the profile of expression of fibroblast growth factor receptors (FGFR), we examined the effects of FGFR tyrosine kinase inhibition using the small mol. FGFR inhibitor PD173074. This inhibitor resulted in abrogation of fibroblast growth factor-1-mediated FGFR4 phosphorylation in TT cells, an effect that was accompanied by significant arrest of cell proliferation and tumor growth in vivo. Moreover, the combination of STI571 and PD173074 resulted in greater suppression of cell proliferation in vitro and tumor control in vivo than that achieved with either agent alone. These data highlight RET and FGFR4 as therapeutic targets and suggest a potential role for the combined use of tyrosine kinase inhibitors in the management of inoperable medullary thyroid cancers.
 ST STI571 PD173074 medullary thyroid cancer antitumor
 IT Antitumor agents
 (STI571 and PD173074 alone and in combination showed antitumor activity by suppressing cell proliferation, reducing tumor volume and weight in human medullary carcinoma TT cell line and in mouse model of medullary thyroid cancer)
 IT Apoptosis
 (STI571 and PD173074 combination showed greater efficacy in

inducing apoptosis than STI571 or PD173074 alone in human medullary carcinoma TT cell line and in mouse model of medullary thyroid cancer)

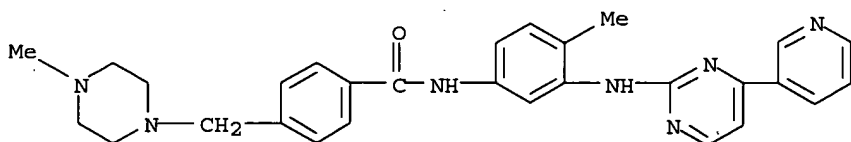
- IT Human
Thyroid gland
(STI571 and PD173074 combination showed greater efficacy in suppressing cell proliferation than STI571 or PD173074 alone in human medullary carcinoma TT cell line and in mouse model of medullary thyroid cancer)
- IT Combination chemotherapy
(combination therapy with STI571 and PD173074 showed greater efficacy in suppressing cell proliferation than STI571 or PD173074 alone in human medullary carcinoma TT cell line and in mouse model of MTC)
- IT Fibroblast growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(fibroblast growth factor receptor inhibitor PD173074 effectively inhibited cell proliferation and FGFR4 phosphorylation in human medullary carcinoma TT cell line and reduced tumor growth in mouse model of medullary thyroid cancer)
- IT Cell proliferation
(inhibition; STI571 and PD173074 combination showed greater efficacy in suppressing cell proliferation than STI571 or PD173074 alone in human medullary carcinoma TT cell line and in mouse model of medullary thyroid cancer)
- IT Thyroid gland, neoplasm
(medullary carcinoma; STI571 and PD173074 combination showed greater efficacy in suppressing cell proliferation than STI571 or PD173074 alone in human medullary carcinoma TT cell line and in mouse model of medullary thyroid cancer)
- IT Carcinoma
(thyroid medullary; STI571 and PD173074 combination showed greater efficacy in suppressing cell proliferation than STI571 or PD173074 alone in human medullary carcinoma TT cell line and in mouse model of medullary thyroid cancer)
- IT Fibroblast growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type 4; fibroblast growth factor receptor inhibitor PD173074 inhibited FGFR4 phosphorylation in human medullary carcinoma TT cell line)
- IT Drug targets
(tyrosine kinase inhibitor STI571 and FGFR inhibitor PD173074 alone and in combination suppressed cell proliferation in human medullary carcinoma TT cell line and in mouse model of medullary thyroid cancer)
- IT 219580-11-7, PD173074
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fibroblast growth factor receptor inhibitor PD173074 effectively inhibited cell proliferation and FGFR4 phosphorylation in human medullary carcinoma TT cell line and reduced tumor growth in mouse model of medullary thyroid cancer)
- IT 146279-92-7, RET receptor tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tyrosine kinase inhibitor STI571 effectively inhibited cell proliferation and RET phosphorylation in human medullary carcinoma TT cell line and reduced tumor growth in mouse model of medullary thyroid cancer)
- IT 220127-57-1, STI571
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor STI571 effectively inhibited cell proliferation and RET phosphorylation in human medullary carcinoma TT cell line and reduced tumor growth in mouse model of medullary thyroid cancer)

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) Boelaert, K; J Clin Endocrinol Metab 2003, V88, P2341 HCAPLUS
 (2) Burris, H; Oncologist 2004, V9(Suppl 3), P10
 (3) Capdeville, R; Nat Rev Drug Discov 2002, V1, P493 HCAPLUS
 (4) Cavallaro, U; Nat Cell Biol 2001, V3, P650 HCAPLUS
 (5) Cohen, M; Surgery 2002, V132, P960
 (6) Cohen, P; Nat Rev Drug Discov 2002, V1, P309 HCAPLUS
 (7) Dackiw, A; Endocrinology (Baltimore) 2004, V145, P5840 HCAPLUS
 (8) Druker, B; J Clin Invest 2000, V105, P3 HCAPLUS
 (9) Druker, B; N Engl J Med 2001, V344, P1031 HCAPLUS
 (10) Dziba, J; J Clin Endocrinol Metab 2004, V89, P2127 HCAPLUS
 (11) Eggo, M; Mol Cell Endocrinol 2003, V213, P47 HCAPLUS
 (12) Eng, C; Hum Mol Genet 1994, V3, P237 HCAPLUS
 (13) Ezzat, S; Biochem Biophys Res Commun 2001, V287, P60 HCAPLUS
 (14) Ezzat, S; J Clin Invest 2002, V109, P69 HCAPLUS
 (15) Ezzat, S; Mol Endocrinol 2004, V18, P2543 HCAPLUS
 (16) Golubovskaya, V; J Biol Chem 2002, V277, P38978 HCAPLUS
 (17) Hughes, S; J Histochem Cytochem 1997, V45, P1005 HCAPLUS
 (18) Jing, S; Cell 1996, V85, P1124
 (19) Koziczak, M; Oncogene 2004, V23, P3501 HCAPLUS
 (20) Mason, I; Cell 1994, V78, P547 MEDLINE
 (21) Mohammadi, M; EMBO J 1998, V17, P5896 HCAPLUS
 (22) Moley, J; Surgery 1993, V114, P1090 MEDLINE
 (23) Mulligan, L; Nat Genet 1994, V6, P70 HCAPLUS
 (24) Mulligan, L; Nature 1993, V363, P458 HCAPLUS
 (25) Onose, H; Eur J Endocrinol 1999, V140, P169 HCAPLUS
 (26) Partanen, J; EMBO J 1991, V10, P1347 HCAPLUS
 (27) Revest, J; Dev Biol 2001, V231, P47 HCAPLUS
 (28) Skaper, S; J Neurochem 2000, V75, P1520 HCAPLUS
 (29) Wells, S; World J Surg 2000, V24, P952
 (30) Xia, W; Oncogene 2002, V21, P6255 HCAPLUS
 (31) Yu, S; Am J Physiol Endocrinol Metab 2002, V283, PE490 HCAPLUS
 IT 146279-92-7, RET receptor tyrosine kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (tyrosine kinase inhibitor STI571 effectively inhibited cell
 proliferation and RET phosphorylation in human medullary carcinoma TT
 cell line and reduced tumor growth in mouse model of medullary thyroid
 cancer)
 RN 146279-92-7 HCAPLUS
 CN Kinase (phosphorylating), gene ret protein (9CI) (CA INDEX NAME)

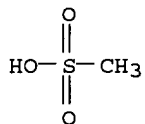
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 220127-57-1, STI571
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity)
 ; THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tyrosine kinase inhibitor STI571 effectively inhibited cell
 proliferation and RET phosphorylation in human medullary carcinoma TT
 cell line and reduced tumor growth in mouse model of medullary thyroid
 cancer)
 RN 220127-57-1 HCAPLUS
 CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-
 pyridinyl)-2-pyrimidinyl]amino]phenyl]-, monomethanesulfonate (9CI) (CA
 INDEX NAME)
 CM 1
 CRN 152459-95-5
 CMF C29 H31 N7 O



CM 2

CRN 75-75-2
CMF C H4 O3 S



L44 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:80505 HCAPLUS
DN 140:122778
ED Entered STN: 01 Feb 2004
TI 4-(4-Methylpiperazin-1-ylmethyl)-N-[4-methyl-3-((4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide for treating mutated-RET kinase associated diseases
IN Fagin, James Alexander
PA University of Cincinnati, USA
SO PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K-0031/506
ICS A61P-0035/00
CC 1-6 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO2004009087	A1	20040129	2003WO-IB01984	20030523 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW				
RW: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR				
CA---2493000	AA	20040129	2003CA-2493000	20030523 <--
AU2003232960	A1	20040209	2003AU-0232960	20030523 <--
EP---1526854	A1	20050504	2003EP-0727759	20030523 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR2003012873	A	20050628	2003BR-0012873	20030523 <--
JP2005535675	T2	20051124	2004JP-0522385	20030523 <--
PRAI 2002US-398409P	P	20020724	<--	
2003WO-IB01984	W	20030523	<--	

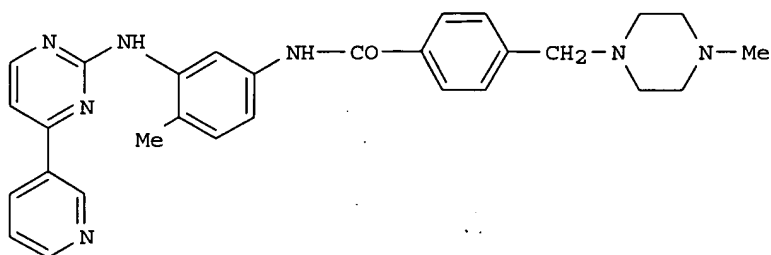
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004009087	ICM	A61K-0031/506
	ICS	A61P-0035/00
	IPCI	A61K0031-506 [ICM,7]; A61P0035-00 [ICS,7]
	IPCR	A61K0031-506 [I,A]; A61K0031-506 [I,C]
	ECLA	A61K031/506 <--
CA---2493000	IPCI	A61K0031-506 [ICM,7]; A61P0035-00 [ICS,7] <--
AU2003232960	IPCI	A61K0031-506 [ICM,7]; A61P0035-00 [ICS,7] <--
EP---1526854	IPCI	A61K0031-506 [ICM,7]; A61P0035-00 [ICS,7] <--
	IPCR	A61K0031-506 [I,A]; A61K0031-506 [I,C] <--
BR2003012873	IPCI	A61K0031-506 [ICM,7]; A61P0035-00 [ICS,7]

```

ECLA      A61K031/506                                <--
JP2005535675 IPCI      A61K0031-506 [ICM,7]; A61P0005-20 [ICS,7]; A61P0017-00
                                [ICS,7]; A61P0035-00 [ICS,7]; A61P0043-00 [ICS,7];
                                C07D0401-04 [ICS,7]
FTERM      4C063/AA01; 4C063/BB01; 4C063/CC31; 4C063/DD12;
                                4C063/EE01; 4C086/AA01; 4C086/AA02; 4C086/BC50;
                                4C086/GA07; 4C086/GA08; 4C086/GA12; 4C086/MA01;
                                4C086/MA04; 4C086/ZB26; 4C086/ZC20                                <--

```



I

AB The invention discloses the use of the title compound (I), or a pharmaceutically acceptable salt thereof, for the treatment of mutated-RET kinase associated disease, especially mutated RET kinase-associated thyroid cancer.

ST RET kinase disease therapeutic benzamide deriv;
thyroid cancer treatment benzamide deriv

IT Intestine, disease
(Hirschsprung's disease; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Phosphorylation, biological
(autophosphorylation; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Drug delivery systems
Human
Hyperparathyroidism
Pheochromocytoma
Thyroid gland, neoplasm
(benzamide derivative for treating mutated-RET kinase associated diseases)

IT Drug delivery systems
(capsules; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Amyloidosis
(cutaneous lichen amyloidosis; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Thyroid gland, neoplasm
(familial medullary carcinoma; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Carcinoma
(familial thyroid medullary; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Parathyroid gland, disease
(hyperplasia; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Thyroid gland, neoplasm
(medullary carcinoma; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Endocrine system, neoplasm
(multiple endocrine neoplasia, type 2; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Endocrine system, neoplasm
(multiple endocrine neoplasia, type 2a; benzamide derivative for treating mutated-RET kinase associated diseases)

mutated-RET kinase associated diseases)

IT Endocrine system, neoplasm
(multiple endocrine neoplasia, type 2b; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Nerve, neoplasm
(neuroma, mucosal neuroma; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Thyroid gland, neoplasm
(papillary carcinoma; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Hyperplasia
(parathyroid; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Carcinoma
(thyroid medullary; benzamide derivative for treating mutated-RET kinase associated diseases)

IT Carcinoma
(thyroid papillary; benzamide derivative for treating mutated-RET kinase associated diseases)

IT 63551-76-8, Phospholipase C γ 146279-92-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(benzamide derivative for treating mutated-RET kinase associated diseases)

IT 152459-95-5 220127-57-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzamide derivative for treating mutated-RET kinase associated diseases)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Fagin, J; ENDOCRINOLOGY 2002, V143(6), P2025 HCAPLUS

(2) Home-Page Of The Washington University School Of Medicine;
<http://www.surgery.wustl.edu/rs/residents.asp?subcategoryid=11&drid=204>
2003

(3) Meric, F; CLINICAL CANCER RESEARCH 2002, V8(2), P361 HCAPLUS

(4) Micha, B; WO---9903854 A 1999 HCAPLUS

IT 146279-92-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(benzamide derivative for treating mutated-RET kinase associated diseases)

RN 146279-92-7 HCAPLUS

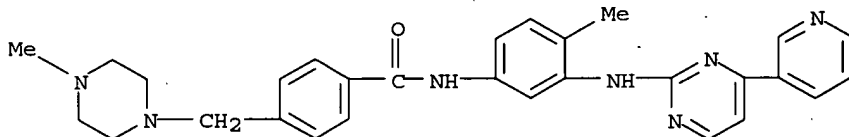
CN Kinase (phosphorylating), gene ret protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 152459-95-5 220127-57-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzamide derivative for treating mutated-RET kinase associated diseases)

RN 152459-95-5 HCAPLUS

CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



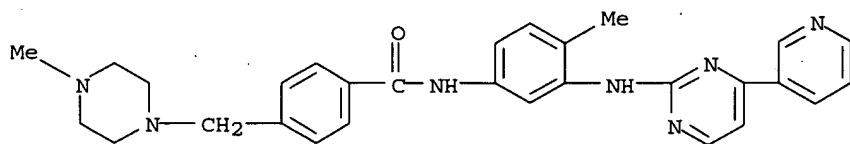
RN 220127-57-1 HCAPLUS

CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 152459-95-5

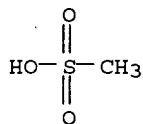
CMF C29 H31 N7 O



CM 2

CRN 75-75-2

CMF C H4 O3 S



L44 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2004:4910 HCAPLUS

DN 140:350141

ED Entered STN: 05 Jan 2004

TI RET tyrosine kinase and medullary thyroid cells are unaffected by clinical doses of STI571

AU Skinner, Michael A.; Safford, Shawn D.; Freemerman, Alex J.

CS Department of Surgery, Duke University, Durham, NC, 27710, USA

SO Anticancer Research (2003), 23(5A), 3601-3606

CODEN: ANTRD4; ISSN: 0250-7005

PB International Institute of Anticancer Research

DT Journal

LA English

CC 1-6 (Pharmacology)

AB Activating mutations in the RET receptor tyrosine kinase are responsible for the development of medullary thyroid cancer (MTC) in persons with Multiple Endocrine Neoplasia type 2. We hypothesized that STI571 (Gleevec) would inhibit RET kinase and be a useful agent in the treatment of MTC. We determined the IC50 of STI571 for RET using an in vitro kinase assay and also examined the effects of STI571 on cellular proliferation and viability in TT cells, a human MTC cell line. The average in vitro IC50 of STI571 for RET is 37 $\mu\text{M} \pm 4 \mu\text{M}$. Addnl., TT cells incubated with 10 μM STI571 for up to 8 days showed no apparent reduction in cell proliferation or viability. Higher concns. of STI571, from 25 to 100 μM , induced necrosis of TT cells. The concns. of STI571 required to significantly inhibit RET and to inhibit TT cell proliferation are not clin. achievable. We conclude that STI571 is not likely to be an effective treatment for MTC.

ST STI571 thyroid cancer RET tyrosine kinase antitumor

IT Antitumor agents
Human

(RET tyrosine kinase and medullary thyroid cells are unaffected by clin. doses of STI571)

IT Thyroid gland, neoplasm

(medullary carcinoma; RET tyrosine kinase and
medullary thyroid cells are unaffected by clin. doses of STI571
)

IT 146279-92-7, RET receptor tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RET tyrosine kinase and medullary thyroid cells
are unaffected by clin. doses of STI571)

IT 220127-57-1, STI571
RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)
(RET tyrosine kinase and medullary thyroid cells
are unaffected by clin. doses of STI571)

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

- (1) Buchdunger, E; Cancer Res 1996, V56, P100 HCAPLUS
- (2) Buchdunger, E; J Pharmacol Exp Ther 2000, V295, P139 HCAPLUS
- (3) Carlomagno, F; Cancer Res 2002, V62, P1077 HCAPLUS
- (4) Carlomagno, F; Cancer Res 2002, V62, P7284 HCAPLUS
- (5) Carroll, M; Blood 1997, V90, P4947 HCAPLUS
- (6) Chen, H; Ann Surg 1998, V227, P887 MEDLINE
- (7) Cohen, M; Surgery 2002, V132, P960
- (8) DeMatteo, R; Ann Surg Oncol 2002, V9, P831
- (9) De Vita, G; Cancer Res 2000, V60, P3727 HCAPLUS
- (10) Druker, B; N Engl J Med 2001, V344, P1031 HCAPLUS
- (11) Druker, B; N Engl J Med 2001, V344, P1038 HCAPLUS
- (12) Druker, B; Nature Med 1996, V2, P561 HCAPLUS
- (13) Evans, D; Seminars Surg Oncol 1999, V16, P50 MEDLINE
- (14) George, D; Seminars in Oncol 2001, V28, P27 MEDLINE
- (15) Giuffrida, D; Annals Oncol 1998, V9, P695 MEDLINE
- (16) Golden, J; Exp Neurol 1999, V158, P504 HCAPLUS
- (17) Golden, J; J Comp Neurol 1998, V398, P139 HCAPLUS
- (18) Greco, A; Int J Cancer 2001, V92, P354 HCAPLUS
- (19) Heinrich, M; Hematopoiesis 2000, V96, P925 HCAPLUS
- (20) Hennequin, L; J Medic Chem 2002, V45, P1300 HCAPLUS
- (21) Komminoth, P; Virchows Arch 1997, V431, P1 HCAPLUS
- (22) Le, H; Cancer J 2000, V6, P50 MEDLINE
- (23) Manie, S; Trends in Genetics 2001, V17, P580 HCAPLUS
- (24) Manning, G; Science 2002, V298, P1912 HCAPLUS
- (25) Murakami, H; Biochem Biophys Res Comm 1999, V262, P68 HCAPLUS
- (26) Savage, G; N Engl J Med 2002, V346, P683
- (27) Shtivelman, E; Nature 1985, V315, P550 HCAPLUS
- (28) Tuveson, D; Oncogene 2001, V20, P5054 HCAPLUS
- (29) Wedge, S; Cancer Res 2002, V62, P4645 HCAPLUS

IT 146279-92-7, RET receptor tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RET tyrosine kinase and medullary thyroid cells
are unaffected by clin. doses of STI571)

RN 146279-92-7 HCAPLUS

CN Kinase (phosphorylating), gene ret protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 220127-57-1, STI571
RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)
(RET tyrosine kinase and medullary thyroid cells
are unaffected by clin. doses of STI571)

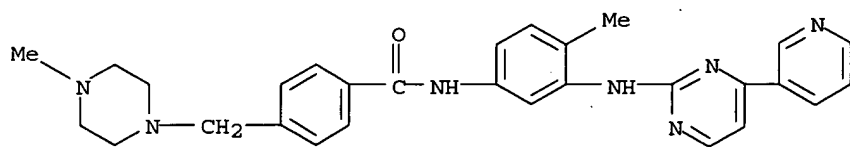
RN 220127-57-1 HCAPLUS

CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 152459-95-5

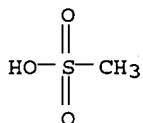
CMF C29 H31 N7 O



CM 2

CRN 75-75-2

CMF C H4 O3 S



L44 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
 AN 2003:640624 HCAPLUS
 DN 140:26084
 ED Entered STN: 18 Aug 2003
 TI Gene abnormality in thyroid cancer
 AU Namba, Hiroyuki; Yamashita, Shunichi
 CS Department of Molecular Medicine, Atomic Bomb Disease Institute, Nagasaki
 University Graduate School of Biomedical Sciences, Japan
 SO Saishin Igaku (2003), 58(7), 1713-1720
 CODEN: SAIGAK; ISSN: 0370-8241
 PB Saishin Igakusha
 DT Journal; General Review
 LA Japanese
 CC 14-0 (Mammalian Pathological Biochemistry)
 Section cross-reference(s): 3
 AB A review. The topics discussed are (1) abnormal Wnt signal transduction
 in thyroid carcinoma; (2) signal transduction pathway targeted treatments
 for thyroid cancer including combined therapy of histone deacetylase
 inhibitor and p53 gene therapy, c-ABL inhibitor STI571 and KDR
 tyrosine kinase inhibitor in blocking RET/PTC activity; and (3)
 mitochondrial DNA mutation in radiation-associated thyroid tumors.
 ST review gene mutation signaling thyroid cancer
 IT Proteins
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (Wnt; abnormalities in the genes involved in Wnt ant RET/PTC signal
 transduction in thyroid cancer)
 IT Mutation
 Signal transduction, biological
 Thyroid gland, neoplasm
 (abnormalities in the genes involved in Wnt ant RET/PTC signal
 transduction in thyroid cancer)
 IT Gene, animal
 Mitochondrial DNA
 p53 (protein)
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (abnormalities in the genes involved in Wnt ant RET/PTC signal
 transduction in thyroid cancer)
 IT 146279-92-7, Gene ret receptor protein tyrosine kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (abnormalities in the genes involved in Wnt ant RET/PTC signal
 transduction in thyroid cancer)
 IT 146279-92-7, Gene ret receptor protein tyrosine kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(abnormalities in the genes involved in Wnt ant RET/PTC signal
transduction in thyroid cancer)

RN 146279-92-7 HCAPLUS

CN Kinase (phosphorylating), gene ret protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> b medl

FILE 'MEDLINE' ENTERED AT 14:51:50 ON 14 MAR 2006

FILE LAST UPDATED: 11 MAR 2006 (20060311/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details
on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).

See also:

<http://www.nlm.nih.gov/mesh/>
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> d all 145 tot

L45 ANSWER 1 OF 2 MEDLINE on STN

AN 2003585757 MEDLINE

DN PubMed ID: 14666655

TI RET tyrosine kinase and medullary thyroid cells are
unaffected by clinical doses of STI571.

AU Skinner Michael A; Safford Shawn D; Freemerman Alex J

CS Department of Surgery, Duke University, Durham, NC 27710, USA.

SO Anticancer research, (2003 Sep-Oct) Vol. 23, No. 5A, pp. 3601-6.
Journal code: 8102988. ISSN: 0250-7005.

CY Greece

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200402

ED Entered STN: 20031216

Last Updated on STN: 20040212

Entered Medline: 20040211

AB BACKGROUND: Activating mutations in the RET receptor tyrosine
kinase are responsible for the development of medullary thyroid
cancer (MTC) in persons with Multiple Endocrine Neoplasia type 2. We
hypothesized that STI571 (Gleevec) would inhibit
RET kinase and be a useful agent in the treatment of
MTC. MATERIALS AND METHODS: We determined the IC50 of STI571
for RET using an in vitro kinase assay and also examined the effects of
STI571 on cellular proliferation and viability in TT cells, a
human MTC cell line. RESULTS: The average in vitro IC50 of STI571
for RET is 37 microM +/- 4 microM. Additionally, TT cells incubated with
10 microM STI571 for up to 8 days showed no apparent reduction
in cell proliferation or viability. Higher concentrations of
STI571, from 25 to 100 microM, induced necrosis of TT cells.
CONCLUSION: The concentrations of STI571 required to

significantly inhibit RET and to inhibit TT cell proliferation are not clinically achievable. We conclude that STI571 is not likely to be an effective treatment for MTC.

CT *Antineoplastic Agents: PD, pharmacology
 *Carcinoma, Medullary: DT, drug therapy
 Carcinoma, Medullary: EN, enzymology
 Carcinoma, Medullary: PA, pathology
 Cell Death: DE, drug effects
 Cell Division: DE, drug effects
 Cell Line, Tumor
 *Enzyme Inhibitors: PD, pharmacology
 Humans
 Inhibitory Concentration 50
 Phosphorylation: DE, drug effects
 *Piperazines: PD, pharmacology
 *Proto-Oncogene Proteins: AI, antagonists & inhibitors
 Proto-Oncogene Proteins: ME, metabolism
 Proto-Oncogene Proteins c-ret
 *Pyrimidines: PD, pharmacology
 *Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors
 Receptor Protein-Tyrosine Kinases: ME, metabolism
 Research Support, Non-U.S. Gov't
 *Thyroid Neoplasms: DT, drug therapy
 Thyroid Neoplasms: EN, enzymology
 Thyroid Neoplasms: PA, pathology
 RN 152459-95-5 (imatinib)
 CN 0 (Antineoplastic Agents); 0 (Enzyme Inhibitors); 0 (Piperazines); 0 (Proto-Oncogene Proteins); 0 (Pyrimidines); EC 2.7.1.112 (Proto-Oncogene Proteins c-ret); EC 2.7.1.112 (Receptor Protein-Tyrosine Kinases)

L45 ANSWER 2 OF 2 MEDLINE on STN
 AN 2003006397 MEDLINE
 DN PubMed ID: 12490842
 TI Inhibition of medullary thyroid carcinoma cell proliferation and RET phosphorylation by tyrosine kinase inhibitors.
 AU Cohen Mark S; Hussain Hamed B; Moley Jeffrey F
 CS Section of Endocrine and Oncologic Surgery, Washington University School of Medicine, St Louis, MO 63110, USA.
 SO Surgery, (2002 Dec) Vol. 132, No. 6, pp. 960-6; discussion 966-7.
 Journal code: 0417347. ISSN: 0039-6060.
 CM Comment in: Surgery. 2004 Feb;135(2):240-1; author reply 241. PubMed ID: 14760839
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals
 EM 200301
 ED Entered STN: 20030107
 Last Updated on STN: 20030124
 Entered Medline: 20030123
 AB BACKGROUND: Most medullary thyroid carcinomas (MTCs) result from gain-of-function mutations in the RET proto-oncogene, which encodes a transmembrane tyrosine kinase receptor. Systemic therapies have not been effective in treating this disease. We evaluated the effects of 3 tyrosine kinase inhibitors (TKIs) on MTC cell growth and RET tyrosine kinase activity by using an in vitro model. METHODS: An MTC cell line (TT cells, RETc634 mutant) cultured in RPMI medium was exposed to varying concentrations of STI571, genistein, or allyl-geldanamycin with controls (no TKI) for 3 to 48 hours. Cellular protein was analyzed by immunoprecipitated Western blot analysis probing with a monoclonal antiphosphotyrosine antibody. Cell proliferation was determined by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) and 5-bromo-2'-deoxyuridine (BrdU) assays. RESULTS: RET phosphorylation was inhibited at 24 hours of exposure to 5 to 20 micromol/L STI571 and 48 hours of exposure to genistein (200 micromol/L) and allyl-geldanamycin (6 micromol/L). RET protein was

detected in equal concentrations in all experimental conditions. MTT and BrdU assays demonstrated a dose-dependent decrease in TT cell proliferation with exposure to the 3 TKIs. CONCLUSIONS: These TKIs selectively inhibit cell growth and **RET** tyrosine kinase activity of MTC cells in vitro in a dose manner. This study suggests the use of TKIs in human trials as a systemic therapy for MTC.

CT *Carcinoma, Medullary
Cell Division: DE, drug effects
*Drosophila Proteins
*Enzyme Inhibitors: PD, pharmacology
Genistein: PD, pharmacology
Humans
Phosphorylation: DE, drug effects
*Piperazines: PD, pharmacology
*Protein-Tyrosine Kinase: AI, antagonists & inhibitors
*Proto-Oncogene Proteins: ME, metabolism
Proto-Oncogene Proteins c-ret
*Pyrimidines: PD, pharmacology
Quinones: PD, pharmacology
*Receptor Protein-Tyrosine Kinases: ME, metabolism
*Thyroid Neoplasms
Tumor Cells, Cultured: CY, cytology
Tumor Cells, Cultured: EN, enzymology
RN 152459-95-5 (imatinib); 30562-34-6 (geldanamycin); 446-72-0 (Genistein)
CN 0 (Drosophila Proteins); 0 (Enzyme Inhibitors); 0 (Piperazines); 0 (Proto-Oncogene Proteins); 0 (Pyrimidines); 0 (Quinones); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.1.112 (Proto-Oncogene Proteins c-ret); EC 2.7.1.112 (Receptor Protein-Tyrosine Kinases); EC 2.7.1.112 (Ret oncogene protein, Drosophila)

=> b embase

FILE 'EMBASE' ENTERED AT 14:51:58 ON 14 MAR 2006
Copyright (c) 2006 Elsevier B.V. All rights reserved.

FILE COVERS 1974 TO 10 Mar 2006 (20060310/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

The updates on February 20 and 24, 2006, were incomplete due to a technical problem. The problem has been corrected, and the missing records were included in the update on March 3, 2006. If you received SDI results from the original updates on February 20 and 24, you will automatically be credited for the update that was rerun on March 3.

If you have any questions, please contact your STN Service Center.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all 147 tot

L47 ANSWER 1 OF 6 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
AN 2005330168 EMBASE
TI **RET** tyrosine kinase signaling in development and cancer.
AU Arighi E.; Borrello M.G.; Sariola H.
CS H. Sariola, Institute of Biomedicine, Biomedicum Helsinki, University of Helsinki, P.O. Box 63, FIN-00014 Helsinki, Finland.
hannu.sariola@helsinki.fi
S0 Cytokine and Growth Factor Reviews, (2005) Vol. 16, No. 4-5, pp. 441-467.
Refs: 372

ISSN: 1359-6101 CODEN: CGFRFB
 PUI S 1359-6101(05)00074-2
 CY United Kingdom
 DT Journal; General Review
 FS 005 General Pathology and Pathological Anatomy
 016 Cancer
 021 Developmental Biology and Teratology
 030 Pharmacology
 037 Drug Literature Index
 LA English
 SL English
 ED Entered STN: 20050901
 Last Updated on STN: 20050901
 AB The variety of diseases caused by mutations in RET receptor tyrosine kinase provides a classic example of phenotypic heterogeneity. Gain-of-function mutations of RET are associated with human cancer. Gene rearrangements juxtaposing the tyrosine kinase domain to heterologous gene partners have been found in sporadic papillary carcinomas of the thyroid (PTC). These rearrangements generate chimeric RET/PTC oncogenes. In the germline, point mutations of RET are responsible for multiple endocrine neoplasia type 2 (MEN 2A and 2B) and familial medullary thyroid carcinoma (FMTC). Both MEN 2 mutations and PTC gene rearrangements potentiate the intrinsic tyrosine kinase activity of RET and, ultimately, activate the RET downstream targets. Loss-of-function mutations of RET cause Hirschsprung's disease (HSCR) or colonic aganglionosis. A deeper understanding of the molecular signaling of normal versus abnormal RET activity in cancer will enable the development of potential new treatments for patients with sporadic and inherited thyroid cancer or MEN 2 syndrome. We now review the role and mechanisms of RET signaling in development and carcinogenesis. .COPYRGT. 2005 Elsevier Ltd. All rights reserved.
 CT Medical Descriptors:
 *development
 *malignant neoplastic disease: DT, drug therapy
 carcinogenesis
 gene
 protein interaction
 papillary carcinoma
 thyroid gland
 gene activation
 thyroid medullary carcinoma: DT, drug therapy
 Hirschsprung disease
 familial cancer
 multiple endocrine neoplasia: DI, diagnosis
 multiple endocrine neoplasia: DT, drug therapy
 Sipple syndrome: DI, diagnosis
 neurofibromatosis: DI, diagnosis
 thyroidectomy
 mutational analysis
 hormone determination
 antineoplastic activity
 thyroid carcinoma: DT, drug therapy
 genetic analysis
 gene mutation
 human
 nonhuman
 review
 priority journal
 Drug Descriptors:
 *protein Ret
 *protein tyrosine kinase
 receptor
 glial cell line derived neurotrophic factor
 ligand
 growth factor
 fibroblast growth factor receptor

radioactive iodine: DT, drug therapy
 imatinib: CB, drug combination
 imatinib: PD, pharmacology
 genistein: PD, pharmacology
 cep 701: DT, drug therapy
 cep 701: PD, pharmacology
 cep 751: DT, drug therapy
 cep 751: PD, pharmacology
 pyrazolopyrimidine derivative: PD, pharmacology
 n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: PD, pharmacology
 quinazoline derivative: PD, pharmacology
 allylgeldanamycin: PD, pharmacology
 geldanamycin: PD, pharmacology
 aryliden 2 indolinone: DT, drug therapy
 aryliden 2 indolinone: PO, oral drug administration
 aryliden 2 indolinone: PD, pharmacology
 indole derivative: DT, drug therapy
 indole derivative: PO, oral drug administration
 indole derivative: PD, pharmacology
 pd 173074: CB, drug combination
 pd 173074: PD, pharmacology
 protein inhibitor: CB, drug combination
 protein inhibitor: PD, pharmacology
 unclassified drug
 RN (protein Ret) 154251-46-4, 158709-11-6; (protein tyrosine kinase)
 80449-02-1; (fibroblast growth factor receptor) 153424-51-2; (
 imatinib) 152459-95-5, 220127-57-1;
 (genistein) 446-72-0; (cep 701) 111358-88-4, 156256-78-9; (cep 751)
 156177-59-2, 199280-60-9; (n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1
 methyl 4 piperidinylmethoxy) 4 quinazolinamine) 443913-73-3;
 (geldanamycin) 30562-34-6
 CN Gleevec; Imatinib; Sti 571; Pd 173074; Cep
 701; Cep 751; Zd 6474
 L47 ANSWER 2 OF 6 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights
 reserved on STN
 AN 2005247109 EMBASE
 TI Vandetanib. Angiogenesis inhibitor VEGFR inhibitor.
 AU Zareba G.; Castaner J.; Bozzo J.
 CS G. Zareba, Prous Science, P.O. Box 540, 08080 Barcelona, Spain
 SO Drugs of the Future, (2005) Vol. 30, No. 2, pp. 138-145. .
 Refs: 39
 ISSN: 0377-8282 CODEN: DRFUD4
 CY Spain
 DT Journal; General Review
 FS 016 Cancer
 030 Pharmacology
 037 Drug Literature Index
 038 Adverse Reactions Titles
 039 Pharmacy
 LA English
 SL English
 ED Entered STN: 20050630
 Last Updated on STN: 20050630
 AB Tumor angiogenesis, or the formation of blood vessels within a tumor,
 plays a key role in cancer cell survival, local tumor growth and the
 development of distant metastases. Vascular endothelial growth factor
 (VEGF) is a potent and specific mitogen for endothelial cells that
 activates angiogenesis and enhances vascular permeability. Vandetanib
 (ZD-6474) is a potent, orally active, low-molecular-weight inhibitor of
 KDR/VEGFR2 tyrosine kinase activity and also displays inhibitory activity
 towards epidermal growth factor receptor (EGFR) tyrosine kinase and
 oncogenic RET kinase. Chronic oral dosing of mice
 bearing human tumor xenografts of diverse tissue origin with vandetanib
 results in dose-dependent inhibition of tumor growth. Vandetanib also

enhanced the antitumor effects of radiation in several tumor models. In phase I trials, vandetanib was well tolerated and was associated with only mild adverse events (skin rash and diarrhea). It is currently in phase II clinical development for a range of solid tumors, both as monotherapy and in combination with certain anticancer agents. Copyright .COPYRGT. 2005 PROUS SCIENCE.

CT

Medical Descriptors:

*tumor vascularization
 *tumor: DT, drug therapy
 *tumor: ET, etiology
 cell survival
 tumor growth
 metastasis: CO, complication
 metastasis: DT, drug therapy
 metastasis: ET, etiology
 endothelium cell
 angiogenesis
 blood vessel permeability
 enzyme inhibition
 long term care
 tumor xenograft
 dose response
 cancer inhibition
 antineoplastic activity
 cancer radiotherapy
 drug tolerability
 side effect: SI, side effect
 rash: SI, side effect
 diarrhea: SI, side effect
 solid tumor: DT, drug therapy
 solid tumor: ET, etiology
 monotherapy
 cancer combination chemotherapy
 thrombocytopenia: SI, side effect
 QT prolongation: SI, side effect
 proteinuria: SI, side effect
 hypertension: SI, side effect
 hematologic disease: SI, side effect
 heart disease: SI, side effect
 desquamation: SI, side effect
 acne: SI, side effect
 photosensitivity: SI, side effect
 gastrointestinal symptom: SI, side effect
 nausea: SI, side effect
 vomiting: SI, side effect
 bone marrow suppression: SI, side effect
 human
 nonhuman
 clinical trial
 phase 1 clinical trial
 review

Drug Descriptors:

*n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: AE, adverse drug reaction
 *n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: CT, clinical trial
 *n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: AD, drug administration
 *n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: AN, drug analysis
 *n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: CB, drug combination
 *n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: DO, drug dose
 *n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: IT, drug interaction

*n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: DT, drug therapy
 *n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: PR, pharmaceutics
 *n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: PK, pharmacokinetics
 *n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: PD, pharmacology
 *n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: PO, oral drug administration
 *vandetanib: AE, adverse drug reaction
 *vandetanib: CT, clinical trial
 *vandetanib: AD, drug administration
 *vandetanib: AN, drug analysis
 *vandetanib: CB, drug combination
 *vandetanib: DO, drug dose
 *vandetanib: IT, drug interaction
 *vandetanib: DT, drug therapy
 *vandetanib: PR, pharmaceutics
 *vandetanib: PK, pharmacokinetics
 *vandetanib: PD, pharmacology
 *vandetanib: PO, oral drug administration
 angiogenesis inhibitor
 vasculotropin receptor
 docetaxel: AE, adverse drug reaction
 docetaxel: CT, clinical trial
 docetaxel: CB, drug combination
 docetaxel: DO, drug dose
 docetaxel: IT, drug interaction
 docetaxel: DT, drug therapy
 docetaxel: PK, pharmacokinetics
 docetaxel: IV, intravenous drug administration
 mitogenic agent
 vasculotropin receptor 2
 protein tyrosine kinase
 protein Ret
 antineoplastic agent: CB, drug combination
 antineoplastic agent: DT, drug therapy
 gefitinib: DV, drug development
 gefitinib: PD, pharmacology
 imatinib: DV, drug development
 imatinib: PD, pharmacology
 unclassified drug
 azd 6474

RN (n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine) 443913-73-3; (vasculotropin receptor) 301253-48-5;
 (docetaxel) 114977-28-5; (protein tyrosine kinase) 80449-02-1; (protein
 Ret) 154251-46-4, 158709-11-6; (gefitinib) 184475-35-2, 184475-55-6,
 184475-56-7; (imatinib) 152459-95-5,
 220127-57-1
 CN (1) Azd 6474; (2) Zd 6474; (3) Zd 1839; (4) Iressa; (5) Sti 571;
 (6) Glivec; (7) Gleevec
 CO (4) Astra Zeneca; (7) Novartis

L47 ANSWER 3 OF 6 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights
 reserved on STN
 AN 2005191925 EMBASE
 TI The RET proto-oncogene: A molecular therapeutic target in thyroid cancer.
 AU Kodama Y.; Asai N.; Kawai K.; Jijiwa M.; Murakumo Y.; Ichihara M.;
 Takahashi M.
 CS M. Takahashi, Department of Pathology, Ctr. for Neurological
 Disease/Cancer, Nagoya Univ. Grad. Sch. of Medicine, 65 Tsurumai-cho,
 Showa-ku, Nagoya 466-8550, Japan. mtakaha@med.nagoya-u.ac.jp
 SO Cancer Science, (2005) Vol. 96, No. 3, pp. 143-148. .
 Refs: 47
 ISSN: 1347-9032 CODEN: CSACCM

CY United Kingdom
 DT Journal; General Review
 FS 003 Endocrinology
 016 Cancer
 030 Pharmacology
 037 Drug Literature Index
 038 Adverse Reactions Titles
 039 Pharmacy
 LA English
 SL English
 ED Entered STN: 20050512
 Last Updated on STN: 20050512
 AB The RET proto-oncogene is responsible for the development of several human inherited and non-inherited diseases. Germline point mutations were identified in multiple endocrine neoplasia types 2A and 2B, and familial medullary thyroid carcinoma. More than 10 rearranged forms of RET, referred to as RET/PTC 1-9, ELKS/RET and RFP/RET, have been cloned from sporadic and radiation-associated papillary thyroid carcinomas. These mutations induced oncogenic activation of RET tyrosine kinase by different mechanisms. To date, various kinds of therapeutic approaches have been developed for the treatment of RET-associated cancers, including tyrosine kinase inhibitors, gene therapy with dominant negative RET mutants, and RNA interference to abrogate oncogenic mutant RET expression. RET and some signaling molecules that function downstream of RET could be potential targets for the development of selective cancer therapeutics. .COPYRGT. Japanese Cancer Association.
 CT Medical Descriptors:
 *thyroid cancer: DT, drug therapy
 *thyroid cancer: ET, etiology
 proto oncogene
 point mutation
 protein function
 neurofibromatosis: DT, drug therapy
 neurofibromatosis: ET, etiology
 Sipple syndrome: DT, drug therapy
 Sipple syndrome: ET, etiology
 thyroid medullary carcinoma: DT, drug therapy
 thyroid medullary carcinoma: ET, etiology
 gene rearrangement
 molecular cloning
 enzyme activation
 viral gene therapy
 RNA interference
 gene expression
 signal transduction
 carcinogenesis
 gene identification
 drug targeting
 enzyme inhibition
 drug efficacy
 drug selectivity
 cancer inhibition
 antineoplastic activity
 side effect: SI, side effect
 cancer resistance
 adenovirus vector
 viral gene delivery system
 human
 nonhuman
 clinical trial
 review
 priority journal
 Drug Descriptors:
 *protein Ret: DT, drug therapy
 *protein Ret: EC, endogenous compound
 *protein Ret: PR, pharmaceuticals

*protein Ret: PD, pharmacology
 protein tyrosine kinase: EC, endogenous compound
 protein tyrosine kinase inhibitor: AE, adverse drug reaction
 protein tyrosine kinase inhibitor: CT, clinical trial
 protein tyrosine kinase inhibitor: DT, drug therapy
 protein tyrosine kinase inhibitor: PD, pharmacology
 protein tyrosine kinase inhibitor: PO, oral drug administration
 imatinib: DT, drug therapy
 imatinib: PD, pharmacology
 n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: AE, adverse drug reaction
 n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: CT, clinical trial
 n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: DT, drug therapy
 n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: PD, pharmacology
 n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4
 quinazolinamine: PO, oral drug administration
 pp 1: PD, pharmacology
 4 amino 7 tert butyl 5 (4 chlorophenyl)pyrazolo[3,4 d]pyrimidine: PD,
 pharmacology
 cep 701: PD, pharmacology
 cep 751: PD, pharmacology
 cep 2563: DT, drug therapy
 cep 2563: PD, pharmacology
 rpi 1: DT, drug therapy
 rpi 1: PD, pharmacology
 rpi 1: PO, oral drug administration
 trastuzumab: DT, drug therapy
 trastuzumab: PD, pharmacology
 cetuximab: CB, drug combination
 cetuximab: DT, drug therapy
 irinotecan: CB, drug combination
 irinotecan: DT, drug therapy
 protein Shc: EC, endogenous compound
 protein Grb2: EC, endogenous compound
 phospholipase C gamma: EC, endogenous compound
 protein kinase B: EC, endogenous compound
 mitogen activated protein kinase p38: EC, endogenous compound
 phosphatidylinositol 3 kinase: EC, endogenous compound
 protein BAD: EC, endogenous compound
 immunoglobulin enhancer binding protein: EC, endogenous compound
 STAT3 protein: EC, endogenous compound
 mucin 1: EC, endogenous compound
 mucin 4: EC, endogenous compound
 mucin 5B: EC, endogenous compound
 guanosine triphosphatase activating protein: EC, endogenous compound
 neurturin: EC, endogenous compound
 artemin: EC, endogenous compound
 unindexed drug
 unclassified drug
 RN (protein Ret) 154251-46-4, 158709-11-6; (protein tyrosine kinase)
 80449-02-1; (imatinib) 152459-95-5,
 220127-57-1; (n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4
 piperidinylmethoxy) 4 quinazolinamine) 443913-73-3; (cep 701) 111358-88-4,
 156256-78-9; (cep 751) 156177-59-2, 199280-60-9; (trastuzumab)
 180288-69-1; (cetuximab) 205923-56-4; (irinotecan) 100286-90-6; (protein
 Shc) 192142-39-5; (protein Grb2) 148266-08-4; (protein kinase B)
 148640-14-6; (phosphatidylinositol 3 kinase) 115926-52-8; (mucin 1)
 212255-06-6; (neurturin) 185830-44-8, 185857-51-6; (artemin) 22149-38-8
 CN Sti 571; Gleevec; Zd 6474; Pp 1; Pp 2; Cep 701; Cep
 751; Cep 2563; Herceptin; Imc c225; Erbitux; Rpi 1

L47 ANSWER 4 OF 6 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights
 reserved on STN

AN 2004236601 EMBASE
 TI Regulation of p27Kip1 protein levels contributes to mitogenic effects of the RET/PTC kinase in thyroid carcinoma cells.
 AU Vitagliano D.; Carlomagno F.; Motti M.L.; Viglietto G.; Nikiforov Y.E.; Nikiforova M.N.; Hershman J.M.; Ryan A.J.; Fusco A.; Melillo R.M.; Santoro M.
 CS M. Santoro, Dipto. di Biol./Patol. Cell./Molec., University 'Federico II', via. S. Pansini 5, 80131 Naples, Italy. masantor@unina.it
 SO Cancer Research, (1 Jun 2004) Vol. 64, No. 11, pp. 3823-3829. .
 Refs: 30
 ISSN: 0008-5472 CODEN: CNREAS
 CY United States
 DT Journal; Article
 FS 003 Endocrinology
 016 Cancer
 037 Drug Literature Index
 LA English
 SL English
 ED Entered STN: 20040628
 Last Updated on STN: 20040628
 AB We show that treatment of a panel of thyroid carcinoma cell lines naturally harboring the RET/PTC1 oncogene, with the RET kinase inhibitors PP1 and ZD6474, results in reversible G(1) arrest. This is accompanied by interruption of Shc and mitogen-activated protein kinase (MAPK) phosphorylation, reduced levels of G(1) cyclins, and increased levels of the cyclin-dependent kinase inhibitor p27Kip1 because of a reduced protein turnover. MAP/extracellular signal-regulated kinase 1/2 inhibition by U0126 caused G1 cyclins down-regulation and p27Kip1 up-regulation as well. Forced expression of RET/PTC in normal thyroid follicular cells caused a MAPK- and proteasome-dependent down-regulation of p27Kip1. Reduction of p27Kip1 protein levels by antisense oligonucleotides abrogated the G(1) arrest induced by RET/PTC blockade. Therefore, in thyroid cancer, RET/PTC-mediated MAPK activation contributes to p27Kip1 deregulation. This pathway is implicated in cell cycle progression and in response to small molecule kinase inhibitors.
 CT Medical Descriptors:
 *protein analysis
 *mitogenesis
 *enzyme activity
 *thyroid carcinoma: ET, etiology
 enzyme inhibition
 cell cycle G1 phase
 mitosis inhibition
 enzyme phosphorylation
 inhibition kinetics
 protein metabolism
 gene expression regulation
 thyroid follicle cell
 human
 controlled study
 human cell
 article
 priority journal
 Drug Descriptors:
 *protein p27: EC, endogenous compound
 *protein p27kip1: EC, endogenous compound
 *proteasome
 *antisense oligonucleotide: PD, pharmacology
 oncoprotein: EC, endogenous compound
 protein Ret: EC, endogenous compound
 protein ptc1: EC, endogenous compound
 protein kinase inhibitor: PD, pharmacology
 protein pp1: PD, pharmacology
 n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4 quinazolinamine: PD, pharmacology
 protein Shc: EC, endogenous compound

cycline: EC, endogenous compound
 1,4 diamino 1,4 bis(2 aminophenylthio) 2,3 dicyanobutadiene: PD,
 pharmacology
 mitogen activated protein kinase 1: EC, endogenous compound
 mitogen activated protein kinase 2: EC, endogenous compound
 mitogen activated protein kinase inhibitor: PD, pharmacology
 imatinib: PD, pharmacology
 broxuridine
 cycloheximide
 unclassified drug

pp 1

RN (protein Ret) 154251-46-4, 158709-11-6; (n (4 bromo 2 fluorophenyl) 6
 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4 quinazolinamine) 443913-73-3;
 (protein Shc) 192142-39-5; (1,4 diamino 1,4 bis(2 aminophenylthio) 2,3
 dicyanobutadiene) 109511-58-2; (mitogen activated protein kinase 1)
 137632-07-6; (mitogen activated protein kinase 2) 137632-08-7; (
 imatinib) 152459-95-5, 220127-57-1;
 (broxuridine) 59-14-3; (cycloheximide) 642-81-9, 66-81-9
 CN (1) Zd 6474; (2) Pp 1; Sti 571; Gleevec; U 0126
 CO (1) Astra Zeneca (United Kingdom); (2) Alexis (United States)

L47 ANSWER 5 OF 6 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights
 reserved on STN

AN 2003489493 EMBASE

TI RET Tyrosine Kinase and Medullary Thyroid Cells are
 Unaffected by Clinical Doses of STI571.

AU Skinner M.A.; Safford S.D.; Freemerman A.J.

CS Dr. A.J. Freemerman, Duke University Medical Center, Box 2627, Durham, NC
 27710, United States. afree@duke.edu

SO Anticancer Research, (2003) Vol. 23, No. 5 A, pp. 3601-3606.
 Refs: 29

ISSN: 0250-7005 CODEN: ANTRD4

CY Greece

DT Journal; Article

FS 003 Endocrinology
 016 Cancer
 030 Pharmacology
 037 Drug Literature Index
 052 Toxicology

LA English

SL English

ED Entered STN: 20040105

Last Updated on STN: 20040105

AB Background: Activating mutations in the RET receptor tyrosine
 kinase are responsible for the development of medullary thyroid
 cancer (MTC) in persons with Multiple Endocrine Neoplasia type 2. We
 hypothesized that STI571 (Gleevec) would inhibit
 RET kinase and be a useful agent in the treatment of
 MTC. Materials and Methods: We determined the IC(50) of STI571
 for RET using an in vitro kinase assay and also examined the effects of
 STI571 on cellular proliferation and viability in TT cells, a
 human MTC cell line. Results: The average in vitro IC(50) of
 STI571 for RET is 37 $\mu\text{M} \pm 4 \mu\text{M}$. Additionally, TT cells
 incubated with 10 μM STI571 for up to 8 days showed no
 apparent reduction in cell proliferation or viability. Higher
 concentrations of STI571, from 25 to 100 μM , induced necrosis
 of TT cells. Conclusion: The concentrations of STI571 required
 to significantly inhibit RET and to inhibit TT cell proliferation are not
 clinically achievable. We conclude that STI571 is not likely to
 be an effective treatment for MTC.

CT Medical Descriptors:

*thyroid medullary carcinoma

thyroid cell

IC 50

assay

cell proliferation

cell viability
 cell death
 drug efficacy
 drug megadose
 dose response
 human
 controlled study
 human cell
 article
 priority journal
 Drug Descriptors:

*imatinib: PD, pharmacology
 *protein Ret: EC, endogenous compound
 *protein tyrosine kinase: EC, endogenous compound
 BCR ABL protein: EC, endogenous compound

RN (imatinib) 152459-95-5, 220127-57-1;
 (protein Ret) 154251-46-4, 158709-11-6; (protein tyrosine kinase)
 80449-02-1
 CN (1) Sti 571
 CO (1) Novartis (United States)

L47 ANSWER 6 OF 6 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

AN 2003011157 EMBASE

TI Inhibition of medullary thyroid carcinoma cell proliferation and RET phosphorylation by tyrosine kinase inhibitors.

AU Cohen M.S.; Hussain H.B.; Moley J.F.

CS Dr. J.F. Moley, Department of Surgery, Washington Univ. School of Medicine, Box 8109, #1 Barnes Hospital Plaza, St. Louis, MO 63110, United States

SO Surgery, (1 Dec 2002) Vol. 132, No. 6, pp. 960-967. .
 Refs: 25

ISSN: 0039-6060 CODEN: SURGAZ

CY United States

DT Journal; Article

FS 016 Cancer

037 Drug Literature Index

LA English

SL English

ED Entered STN: 20030129

Last Updated on STN: 20030129

AB Background. Most medullary thyroid carcinomas (MTCs) result from gain-of-function mutations in the RET proto-oncogene, which encodes a transmembrane tyrosine kinase receptor. Systemic therapies have not been effective in treating this disease. We evaluated the effects of 3 tyrosine kinase inhibitors (TKIs) on MTC cell growth and RET tyrosine kinase activity by using an in vitro model. Methods. An MTC cell line (TT cells, RETc634 mutant) cultured in RPMI medium was exposed to varying concentrations of STI571, genistein, or allyl-geldanamycin with controls (no TKI) for 3 to 48 hours. Cellular protein was analyzed by immunoprecipitated Western blot analysis probing with a monoclonal antiphosphotyrosine antibody. Cell proliferation was determined by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) and 5-bromo-2'-deoxyuridine (BrdU) assays. Results. RET phosphorylation was inhibited at 24 hours of exposure to 5 to 20 μ mol/L STI571 and 48 hours of exposure to genistein (200 μ mol/L) and allyl-geldanamycin (6 μ mol/L). RET protein was detected in equal concentrations in all experimental conditions. MTT and BrdU assays demonstrated a dose-dependent decrease in TT cell proliferation with exposure to the 3 TKIs. Conclusions. These TKIs selectively inhibit cell growth and RET tyrosine kinase activity of MTC cells in vitro in a dose manner. This study suggests the use of TKIs in human trials as a systemic therapy for MTC.

CT Medical Descriptors:

*thyroid medullary carcinoma
 *cancer inhibition

cancer cell culture
 gene mutation
 proto oncogene
 cancer growth
 enzyme activity
 Western blotting
 cell proliferation
 dose response
 enzyme inhibition
 protein phosphorylation
 cytotoxicity
 human
 controlled study
 human cell
 article
 priority journal
 Drug Descriptors:
 *protein Ret
 *tyrosine kinase receptor
 *protein tyrosine kinase inhibitor: PD, pharmacology
 *protein tyrosine kinase
 *imatinib: PD, pharmacology
 *genistein: PD, pharmacology
 antibiotic agent: PD, pharmacology
 geldanamycin derivative: PD, pharmacology
 monoclonal antibody
 phospholipid antibody
 unclassified drug

RN (protein Ret) 154251-46-4, 158709-11-6; (protein tyrosine kinase)
 80449-02-1; (imatinib) 152459-95-5,
 220127-57-1; (genistein) 446-72-0
 CN St 1571

=> b biosis

FILE 'BIOSIS' ENTERED AT 14:52:13 ON 14 MAR 2006
 Copyright (c) 2006 The Thomson Corporation

FILE COVERS 1969 TO DATE.
 CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
 FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 9 March 2006 (20060309/ED)

=> d all 141 tot

L41 ANSWER 1 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
 AN 2005:158712 BIOSIS
 DN PREV200500156517
 TI Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway
 activation in thyroid cancer.
 AU Ciampi, Raffaele; Knauf, Jeffrey A.; Kerler, Roswitha; Gandhi, Manoj; Zhu,
 Zhaowen; Nikiforova, Marina N.; Rabes, Hartmut M.; Fagin, James A.
 ; Nikiforov, Yuri E. [Reprint Author]
 CS Dept Pathol, Univ Cincinnati, 231 Albert Sabin Way, POB 670529, Cincinnati,
 OH, 45267, USA
 Yuri.Nikiforov@uc.edu
 SO Journal of Clinical Investigation, (January 2005) Vol. 115, No. 1, pp.
 94-101. print.
 CODEN: JCINAO. ISSN: 0021-9738.
 DT Article
 LA English
 ED Entered STN: 27 Apr 2005
 Last Updated on STN: 27 Apr 2005
 AB Genes crucial for cancer development can be mutated via various

mechanisms, which may reflect the nature of the mutagen. In thyroid papillary carcinomas, mutations of genes coding for effectors along the MAPK pathway are central for transformation. BRAF point mutation is most common in sporadic tumors. By contrast, radiation-induced tumors are associated with paracentric inversions activating the receptor tyrosine kinases RET and NTRK1. We report here a rearrangement of BRAF via paracentric inversion of chromosome 7q resulting in an in-frame fusion between exons 1-8 of the AKAP9 gene and exons 9-18 of BRAF. The fusion protein contains the protein kinase domain and lacks the autoinhibitory N-terminal portion of BRAF. It has elevated kinase activity and transforms NIH3T3 cells, which provides evidence, for the first time to our knowledge, of in vivo activation of an intracellular effector along the MAPK pathway by recombination. The AKAP9-BRAF fusion was preferentially found in radiation-induced papillary carcinomas developing after a short latency, whereas BRAF point mutations were absent in this group. These data indicate that in thyroid cancer, radiation activates components of the MAPK pathway primarily through chromosomal paracentric inversions, whereas in sporadic forms of the disease, effectors along the same pathway are activated predominantly by point mutations.

CC Genetics - General 03502
 Genetics - Animal 03506
 Genetics - Human 03508
 Pathology - General 12502
 Endocrine - General 17002
 Endocrine - Thyroid 17018
 Neoplasms - Pathology, clinical aspects and systemic effects 24004

IT Major Concepts
 Clinical Endocrinology (Human Medicine, Medical Sciences); Molecular Genetics (Biochemistry and Molecular Biophysics); Oncology (Human Medicine, Medical Sciences)

IT Parts, Structures, & Systems of Organisms
 chromosome 7

IT Diseases
 thyroid carcinoma: endocrine disease/thyroid, neoplastic disease, genetics, pathology
 Thyroid Neoplasms (MeSH); Carcinoma (MeSH)

IT Chemicals & Biochemicals
 MAPK pathway; NTRK1: receptor tyrosine kinase; RET: receptor tyrosine kinase

ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 human (common)
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
 Muridae 86375
 Super Taxa
 Rodentia; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 NIH3T3 cell line (cell line)
 Taxa Notes
 Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

GEN human AKAP9 gene (Hominidae); human BRAF gene (Hominidae): point mutation

L41 ANSWER 2 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
 AN 2005:84450 BIOSIS
 DN PREV200500084456
 TI RET signals through focal adhesion kinase in medullary thyroid cancer cells.
 AU Panta, Ganesh R.; Nwariaku, Fiemu; Kim, Lawrence T. [Reprint Author]
 CS Cent Arkansas Vet Healthcare SystSurg Serv 112, Univ Arkansas Med Sci, 4300 W 7th St, Little Rock, AR, 72205, USA

SO Surgery (St Louis), (December 2004) Vol. 136, No. 6, pp. 1212-1216. print.
ISSN: 0039-6060 (ISSN print).

DT Article

LA English

ED Entered STN: 23 Feb 2005
Last Updated on STN: 23 Feb 2005

AB Background. The RET proto-oncogene is implicated in medullary thyroid cancer (MTC) and has been shown to signal indirectly to focal adhesion kinase (FAK) in cell types other than MTC. We have previously shown that FAK is phosphorylated in MTC cells. We hypothesized that inhibition of RET with pharmacologic inhibitors or by depletion with siRNA would decrease FAK phosphorylation in MTC cells, thereby implicating a RET-FAK signaling pathway. Methods. Human MTC cells (77 cells) were treated with pharmacologic inhibitors or transfected with RET siRNA. Total protein was detected by immunoblotting. Phosphorylated FAK was detected by immunoprecipitating total FAK and immunoblotting with antiphosphotyrosine. Results. Treatment of MTC cells with the inhibitor PP2 significantly inhibited RET phosphorylation and, to a lesser extent, 1,FAK phosphorylation. Imatinib mesylate inhibited FAK phosphorylation only at high doses. RET siRNA significantly decreased RET expression and FAK phosphorylation. Conclusions. RET signals through FAK in MTC cells. Whether this is due to a direct or indirect interaction is not yet clear. PP2 or a similar inhibitor might be a useful treatment for MTC.

CC Genetics - General 03502
Genetics - Human 03508
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Endocrine - General 17002
Endocrine - Thyroid 17018
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Methods and Techniques; Molecular Genetics (Biochemistry and Molecular Biophysics); Pharmacology; Tumor Biology

IT Parts, Structures, & Systems of Organisms
thyroid: endocrine system

IT Diseases
medullary thyroid cancer: endocrine disease/thyroid, neoplastic disease, genetics
Thyroid Neoplasms (MeSH)

IT Chemicals & Biochemicals
PP2: enzyme inhibitor-drug; antiphosphotyrosine; focal adhesion kinase [FAK] [EC 2.7.1.112]: phosphorylation; imatinib mesylate: antineoplastic-drug, enzyme inhibitor-drug, dosage; small interference RNA [siRNA]

IT Methods & Equipment
immunoblotting: immunologic techniques, laboratory techniques; immunoprecipitation: immunologic techniques, laboratory techniques; transfection: genetic techniques, laboratory techniques

IT Miscellaneous Descriptors
RET-focal adhesion kinase signaling pathway
[RET-FAK signaling pathway]

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
TT cell line (cell line)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 144114-16-9 (focal adhesion kinase)

80449-02-1 (focal adhesion kinase)
 144114-16-9 (FAK)
 80449-02-1 (FAK)
 144114-16-9 (EC 2.7.1.112)
 80449-02-1 (EC 2.7.1.112)
 220127-57-1 (imatinib mesylate)
 GEN human RET gene (Hominidae): expression, proto-oncogene

L41 ANSWER 3 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
 AN 2004:55239 BIOSIS
 DN PREV200400058849
 TI RET tyrosine kinase and medullary thyroid cells are
 unaffected by clinical doses of STI571.
 AU Skinner, Michael A.; Safford, Shawn D.; Freemerman, Alex J. [Reprint
 Author]
 CS Duke University Medical Center, Box 2627, Durham, NC, 27710, USA
 afree@duke.edu
 SO Anticancer Research, (September-October 2003) Vol. 23, No. 5A, pp.
 3601-3606. print.
 CODEN: ANTRD4. ISSN: 0250-7005.
 DT Article
 LA English
 ED Entered STN: 21 Jan 2004
 Last Updated on STN: 21 Jan 2004
 AB Background: Activating mutations in the RET receptor tyrosine
 kinase are responsible for the development of medullary thyroid
 cancer (MTC) in persons with Multiple Endocrine Neoplasia type 2. We
 hypothesized that STI571 (Gleevec) would inhibit
 RET kinase and be a useful agent in the treatment of
 MTC. Materials and Methods: We determined the IC50 of STI571
 for RET using an in vitro kinase assay and also examined the effects of
 STI571 on cellular proliferation and viability in TT cells, a
 human MTC cell line. Results: The average in vitro IC50 of STI571
 for RET is 37 μM \pm 4 μM . Additionally, TT cells incubated with 10 μM
 STI571 for up to 8 days showed no apparent reduction in cell
 proliferation or viability. Higher concentrations of STI571,
 from 25 to 100 μM , induced necrosis of TT cells. Conclusion: The
 concentrations of STI571 required to significantly inhibit RET
 and to inhibit TT cell proliferation are not clinically achievable. We
 conclude that STI571 is not likely to be an effective treatment
 for MTC.
 CC Cytology - General 02502
 Cytology - Human 02508
 Enzymes - General and comparative studies: coenzymes 10802
 Pathology - Therapy 12512
 Endocrine - General 17002
 Endocrine - Thyroid 17018
 Pharmacology - General 22002
 Pharmacology - Clinical pharmacology 22005
 Neoplasms - Pathology, clinical aspects and systemic effects 24004
 Neoplasms - Therapeutic agents and therapy 24008
 Tissue culture, apparatus, methods and media 32500
 IT Major Concepts
 Cell Biology; Endocrine System (Chemical Coordination and Homeostasis);
 Enzymology (Biochemistry and Molecular Biophysics); Oncology (Human
 Medicine, Medical Sciences); Pharmacology
 IT Parts, Structures, & Systems of Organisms
 medullary thyroid cells: endocrine system, in-vitro culture, negative
 antitumor drug treatment effects
 IT Diseases
 medullary thyroid carcinoma: endocrine disease/thyroid, neoplastic
 disease, therapy
 Thyroid Neoplasms (MeSH); Carcinoma (MeSH)
 IT Chemicals & Biochemicals
 Gleevec [ST 1571]: antineoplastic-drug; RET
 receptor tyrosine kinase: negative antitumor drug treatment

effects, thyroid cell activity, tumor activity

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): normal subjects, patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 152459-95-5 (Gleevec).
152459-95-5 (ST 1571)
146279-92-7 (RET receptor tyrosine kinase)

L41 ANSWER 4 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2003:355625 BIOSIS
DN PREV200300355625
TI RET/PTC-induced dedifferentiation of thyroid cells is mediated through
Y1062 signaling through SHC-RAS-MAP kinase.
AU Knauf, Jeffrey A. [Reprint Author]; Kuroda, Hiroaki; Basu, Saswata;
Fagin, James A.
CS Division of Endocrinology and Metabolism, College of Medicine, University
of Cincinnati, Mail Location 0547, Cincinnati, OH, 45267-0547, USA
Jeffrey.Knauf@UC.EDU
SO Oncogene, (10 July 2003) Vol. 22, No. 28, pp. 4406-4412. print.
ISSN: 0950-9232 (ISSN print).
DT Article
LA English
ED Entered STN: 6 Aug 2003
Last Updated on STN: 18 Sep 2003

AB Constitutive activation of the RET proto-oncogene in papillary thyroid
carcinomas results from rearrangements linking the promoter(s) and
N-terminal domains of unrelated genes to the C-terminus of RET
tyrosine kinase (RET/PTC). RET/PTC expression has been
demonstrated to inhibit transcription of thyroid-specific genes. To study
the signal transduction pathways responsible for this, we generated PCCL3
thyroid cells with doxycycline-inducible expression of RET/PTC3,
RET/PTC3Y541F, or PTC2/PDZ. Acute expression of RET/PTC3Y541F
appropriately interacted with Shc, an intermediate in the activation of
the Ras pathway, but failed to activate PLCgamma. By contrast, PTC2/PDZ
failed to bind Shc, but interacted normally with PLCgamma. Acute
expression of RET/PTC3 or RET/PTC3Y541F, but not PTC2/PDZ, inhibited
TSH-induced Tg and NIS expression, suggesting that activation of Shc-Ras,
but not PLCgamma, is required for RET/PTC-induced dedifferentiation.
Accordingly, acute expression of H-RasV12 or of a constitutively active
MEK1 also blocked TSH-induced expression of Tg and NIS. Moreover, MEK
inhibitors restored Tg and NIS levels. In conclusion, activation of the
Ras/Raf/MEK/MAPK pathway through Shc mediates RET/PTC-induced thyroid cell
dedifferentiation. This suggests that inhibition of this pathway may
promote redifferentiation in poorly differentiated thyroid carcinomas with
constitutive activation of either Ras or RET/PTC.

CC Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Endocrine - General 17002
Endocrine - Thyroid 17018
Neoplasms - Pathology, clinical aspects and systemic effects 24004

IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Enzymology
(Biochemistry and Molecular Biophysics)

IT Parts, Structures, & Systems of Organisms
thyroid cell: endocrine system, dedifferentiation

IT Diseases
papillary thyroid carcinoma: endocrine disease/thyroid, neoplastic

disease, PTC
Thyroid Neoplasms (MeSH); Carcinoma (MeSH)

IT Chemicals & Biochemicals
MAP kinase [mitogen-activated protein kinase] [EC 2.7.1.37]; MEK1;
PLC-gamma [phospholipase C-gamma]; RET tyrosine
kinase [EC 2.7.1.112]; Ras; Shc; Y1062; doxycycline;
thyroglobulin

IT Methods & Equipment
Northern blot: genetic techniques, laboratory techniques

IT Miscellaneous Descriptors
gene expression; signal transduction pathways

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
PCCL3 cell line (cell line): human thyroid cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 142243-02-5 (MAP kinase)
9026-43-1 (MAP kinase)
142243-02-5 (mitogen-activated protein kinase)
9026-43-1 (mitogen-activated protein kinase)
142243-02-5 (EC 2.7.1.37)
9026-43-1 (EC 2.7.1.37)
63551-76-8 (PLC-gamma)
63551-76-8 (phospholipase C-gamma)
80449-02-1 (RET tyrosine kinase)
80449-02-1 (EC 2.7.1.112)
564-25-0 (doxycycline)

GEN human RET gene (Hominidae): proto-oncogene

L41 ANSWER 5 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2003:197536 BIOSIS
DN PREV200300197536
TI High prevalence of BRAF mutations in thyroid cancer: Genetic evidence for
constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in
papillary thyroid carcinoma.

AU Kimura, Edna T.; Nikiforova, Marina N.; Zhu, Zhaowen; Knauf, Jeffrey A.;
Nikiforov, Yuri E.; Fagin, James A. [Reprint Author]

CS Division of Endocrinology and Metabolism, College of Medicine, University
of Cincinnati, Cincinnati, OH, 45267-0547, USA
james.fagin@uc.edu

SO Cancer Research, (April 1 2003) Vol. 63, No. 7, pp. 1454-1457. print.
ISSN: 0008-5472 (ISSN print).

DT Article
LA English
ED Entered STN: 23 Apr 2003
Last Updated on STN: 23 Apr 2003

AB Thyroid papillary cancers (PTCs) are associated with activating mutations
of genes coding for RET or TRK tyrosine kinase receptors, as well as of
RAS genes. Activating mutations of BRAF were reported recently in most
melanomas and a small proportion of colorectal tumors. Here we show that
a somatic mutation of BRAF, V599E, is the most common genetic change in
PTCs (28 of 78; 35.8%). BRAFV599E mutations were unique to PTCs, and not
found in any of the other types of differentiated follicular neoplasms
arising from the same cell type (0 of 46). Moreover, there was no overlap
between PTC with RET/PTC, BRAF, or RAS mutations, which altogether were
present in 66% of cases. The lack of concordance for these mutations was
highly unlikely to be a chance occurrence. Because these signaling
proteins function along the same pathway in thyroid cells, this represents
a unique paradigm of human tumorigenesis through mutation of three
signaling effectors lying in tandem.

CC Cytology - Animal 02506
Cytology - Human 02508
Genetics - Human 03508

Digestive system - Pathology 14006
 Endocrine - General 17002
 Endocrine - Thyroid 17018
 Neoplasms - Pathology, clinical aspects and systemic effects 24004.

IT Major Concepts
 Clinical Endocrinology (Human Medicine, Medical Sciences); Medical Genetics (Allied Medical Sciences); Oncology (Human Medicine, Medical Sciences)

IT Parts, Structures, & Systems of Organisms
 thyroid cell: endocrine system

IT Diseases
 colorectal tumor: digestive system disease, neoplastic disease
 Colorectal Neoplasms (MeSH)

IT Diseases
 papillary thyroid carcinoma: endocrine disease/thyroid, neoplastic disease
 Thyroid Neoplasms (MeSH); Carcinoma (MeSH)

IT Diseases
 thyroid cancer: endocrine disease/thyroid, neoplastic disease
 Thyroid Neoplasms (MeSH)

IT Chemicals & Biochemicals
 RET: tyrosine kinase receptor; TRK: tyrosine kinase receptor; signaling proteins

IT Miscellaneous Descriptors
 tumorigenesis

ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 NCI-H1755 cell line (cell line): human non-small cell lung cancer
 NPA cell line (cell line): human thyroid carcinoma cells
 SKMel cell line (cell line): human melanoma cells
 WRO cell line (cell line): human thyroid follicular carcinoma
 human (common): patient
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

GEN human BRAF gene (Hominidae); human RAS gene (Hominidae)

L41 ANSWER 6 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
 AN 2003:111240 BIOSIS
 DN PREV200300111240
 TI Inhibition of medullary thyroid carcinoma cell proliferation and RET phosphorylation by tyrosine kinase inhibitors.
 AU Cohen, Mark S.; Hussain, Hamed B.; Moley, Jeffrey F. [Reprint Author]
 CS Surgery, Washington University School of Medicine, No. 1 Barnes Hospital Plaza, 5108 Queeny Tower, Box 8109, Saint Louis, MO, 63110, USA
 SO Surgery (St Louis), (December 2002) Vol. 132, No. 6, pp. 960-967. print. ISSN: 0039-6060 (ISSN print).
 DT Article
 LA English
 ED Entered STN: 26 Feb 2003
 Last Updated on STN: 26 Feb 2003
 AB Background: Most medullary thyroid carcinomas (MTCs) result from gain-of-function mutations in the RET proto-oncogene, which encodes a transmembrane tyrosine kinase receptor. Systemic therapies have not been effective in treating this disease. We evaluated the effects of 3 tyrosine kinase inhibitors (TKIs) on MTC cell growth and RET tyrosine kinase activity by using an in vitro model. Methods: An MTC cell line (TT cells, RETc634 mutant) cultured in RPMI medium was exposed to varying concentrations of STI571, genistein, or allyl-geldanamycin with controls (no TKI) for 3 to 48 hours. Cellular protein was analyzed by immunoprecipitated Western blot analysis probing with a monoclonal antiphosphotyrosine antibody. Cell proliferation was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and 5-bromo-2'-deoxyuridine (BrdU) assays. Results: RET

phosphorylation was inhibited at 24 hours of exposure to 5 to 20 $\mu\text{mol/L}$ STI571 and 48 hours of exposure to genistein (200 $\mu\text{mol/L}$) and allyl-geldanamycin (6 $\mu\text{mol/L}$). RET protein was detected in equal concentrations in all experimental conditions. MTT and BrdU assays demonstrated a dose-dependent decrease in TT cell proliferation with exposure to the 3 TKIs. Conclusions: These TKIs selectively inhibit cell growth and RET tyrosine kinase activity of MTC cells in vitro in a dose manner. This study suggests the use of TKIs in human trials as a systemic therapy for MTC.

CC Cytology - General 02502
 Cytology - Human 02508
 Genetics - General 03502
 Genetics - Human 03508
 Biochemistry studies - General 10060
 Enzymes - General and comparative studies: coenzymes 10802
 Endocrine - General 17002
 Endocrine - Thyroid 17018
 Neoplasms - Pathology, clinical aspects and systemic effects 24004

IT Major Concepts
 Cell Biology; Endocrine System (Chemical Coordination and Homeostasis);
 Genetics; Tumor Biology

IT Diseases
 medullary thyroid carcinoma: endocrine disease/thyroid, neoplastic
 disease
 Thyroid Neoplasms (MeSH); Carcinoma (MeSH)

IT Chemicals & Biochemicals
 RET: tyrosine kinase, phosphorylation; STI571:
 tyrosine kinase inhibitor; allyl-geldanamycin: tyrosine kinase
 inhibitor; genistein: tyrosine kinase inhibitor

ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 TT cell line (cell line): human medullary thyroid carcinoma cells,
 proliferation
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 446-72-0 (genistein)

GEN human RET gene (Hominidae): proto-oncogene

=> d his

(FILE 'HOME' ENTERED AT 14:13:24 ON 14 MAR 2006)

FILE 'HCAPLUS' ENTERED AT 14:13:39 ON 14 MAR 2006

L1 1 (US2005-521927 OR WO2003-IB1984 OR US2002-398409#)/AP, PRN
 L2 1 (US2006-521927 OR WO2003-IB1984 OR US2002-398409#)/AP, PRN
 L3 5326 NOVARTIS/CS, PA
 E FAGIN J/AU
 L4 108 E3-7

FILE 'REGISTRY' ENTERED AT 14:16:24 ON 14 MAR 2006

FILE 'HCAPLUS' ENTERED AT 14:16:27 ON 14 MAR 2006

L5 TRA L1 1- RN : 4 TERMS

FILE 'REGISTRY' ENTERED AT 14:16:28 ON 14 MAR 2006

L6 4 SEA L5
 L7 143 C29H31N7O
 L8 68 L7 AND (NC5 AND NCNC3 AND NC2NC2)/ES AND >=2 46.150.18/RID
 L9 19 L8 NOT (COMPD OR MIXT OR COMPOUND OR UNSPECIFIED OR (MXS OR IDS

FILE 'HCAPLUS' ENTERED AT 14:20:36 ON 14 MAR 2006

L10 1681 L9

L11 71 L10 AND L1-4
L12 1771 CGP57148# OR CGP () (57148 OR 57 148) OR GLEEVIC OR GLIVEC OR IM

FILE 'REGISTRY' ENTERED AT 14:29:23 ON 14 MAR 2006
L13 37 (RET (L)KINASE#)/CNS

FILE 'HCAPLUS' ENTERED AT 14:30:15 ON 14 MAR 2006
L14 513 L13
L15 451 S RET (2W)KINASE#
L16 1576 L10,L12 (L) (PAC OR THU)/RL
L17 5 L16 AND L14-15
L18 2 L17 AND L1-4
L19 21952 (UNIV? (1W)CINCI?)/PA,CS
L20 1 L16 AND L19
L21 2 L18,L20
L22 3 L17 NOT L21

FILE 'MEDLINE' ENTERED AT 14:38:29 ON 14 MAR 2006
L23 2582 L10,L12
L24 274 L14-15
L25 2 L23 AND L24

FILE 'HCAPLUS' ENTERED AT 14:40:21 ON 14 MAR 2006
L26 5 L17-18,L20-22
L27 2 L26 AND L1-4
L28 5 L26 AND L10-12
L29 5 L26 AND L14-22
L30 5 L27-29

FILE 'EMBASE' ENTERED AT 14:41:27 ON 14 MAR 2006
L31 5141 L23
L32 255 L14-15
L33 6 L31 AND L32

FILE 'BIOSIS' ENTERED AT 14:45:23 ON 14 MAR 2006
L34 2 L23 AND L24
E FAGIN J/AU
L35 192 E3-7
L36 0 L35 AND L23
L37 3 L35 AND L24
L38 961 STI571
L39 430 STI 571
L40 2 L38-39 AND L24
L41 6 L34,L37,L40

FILE 'HCAPLUS' ENTERED AT 14:47:48 ON 14 MAR 2006
L42 3 L38-39 AND L14-15

FILE 'MEDLINE' ENTERED AT 14:48:22 ON 14 MAR 2006
L43 2 L38-39 AND L14-15

FILE 'HCAPLUS' ENTERED AT 14:48:54 ON 14 MAR 2006
L44 6 L30,L42

FILE 'MEDLINE' ENTERED AT 14:49:03 ON 14 MAR 2006
L45 2 L25,L43

FILE 'EMBASE' ENTERED AT 14:50:07 ON 14 MAR 2006
L46 6 L43
L47 6 L46,L33

=>